PREVENTING ANOTHER SV40 TRAGEDY: ARE TODAY'S VACCINE SAFETY PROTOCOLS EFFECTIVE?

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RIGHTS AND WELLNESS

OF THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED EIGHTH CONGRESS

FIRST SESSION

NOVEMBER 13, 2003

Serial No. 108–127

Printed for the use of the Committee on Government Reform

Available via the World Wide Web: http://www.gpo.gov/congress/house
http://www.house.gov/reform

U.S. GOVERNMENT PRINTING OFFICE

92–772 PDF WASHINGTON : 2004

For sale by the Superintendent of Documents, U.S. Government Printing Office
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PREVENTING ANOTHER SV40 TRAGEDY: ARE TODAY'S VACCINE SAFETY PROTOCOLS EFFECTIVE?

THURSDAY, NOVEMBER 13, 2003

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RIGHTS AND WELLNESS,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The subcommittee met, pursuant to notice, at 2 p.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the subcommittee) presiding.

Present: Representatives Burton and Davis.

Staff present: Mark Walker, chief of staff; Mindi Walker and Brian Fauls, professional staff members; Nick Mutton, press secretary; Danielle Perraut, clerk; Richard Butcher, minority counsel; and Jean Gosa, minority assistant clerk.

Mr. BURTON. Good afternoon. A quorum being present, the Subcommittee on Human Rights and Wellness will come to order and I ask unanimous consent that all Members and witnesses' written and opening statements be included in the record, and without objection so ordered.

I ask unanimous consent that all articles, exhibits and extraneous or tabular material referred to be included in the record. Without objection so ordered.

Today the subcommittee is holding the second in a series of hearings examining the aftermath of the tragedy of SV40 contamination of America's poliovirus vaccine supply in the 1950's and early 1960's. During the first half of the 20th century, polio struck down hundreds of thousands of people leaving many paralyzed, and I knew some of those people, some in iron lung machines and killing many thousands of others.

The worst year for the disease in the United States was 1952, when more than 57,000 polio cases were reported and at least 300,000 or 3,000 of those individuals died.

Following the licensure of the Salk polio vaccine in 1955, the incidence of the disease fell dramatically. The disease was further reduced by the advent of the Sabin oral polio vaccine in 1961. In fact, the last cases of paralytic polio from natural poliovirus in the United States were in 1979 and the most recent case from outside the United States occurred in 1993. Today polio has virtually been eliminated from the United States and the entire Western Hemisphere, although it remains a threat in some developing countries.

There can be little doubt that the invention of the vaccine immunization to protect children and adults from infectious diseases, as demonstrated by the success of the anti-polio campaign, was one of the greatest public health achievements of the 20th century. Nobody takes issue with that. In fact immunization as a tool against disease in general has been so successful that it has now become almost commonplace to use it against even relative minor diseases such as human influenza.

As a society we have been so confident in the power of vaccines that we even create government mandates requiring vaccinations be administered before admitting individuals to daycare, public schools, college or the military. But what we perhaps tend to forget is that immunization is very different than administering a medicine to combat an active illness in a person. Instead of curing a disease, vaccines instead introduce a potentially disease causing agent into an otherwise healthy body in order to stimulate an immune response. Thus, there are always risks associated with taking any vaccine, and I think most people realize that.

In some cases vaccines have been known to cause the very disease they were created to prevent. But the risk can be greater still. In the earliest days of the polio vaccine production, laboratory tests were not sophisticated enough to detect the presence of what became known as Simian Virus 40 [SV40]. At least 26 other Simian contaminants were detected and eliminated. But SV40 slipped past quality control testing procedures and into the vaccine pool, potentially infecting millions of Americans.

Soon after its discovery, scientists also learned that SV40 could cause cancerous tumors in hamsters. So in society's zeal to combat one disease we as a society potentially risked exposing millions of Americans to another deadly disease.

As the subcommittee learned at our last SV polio hearing on September 10th, we are still trying to uncover the true health impact of the SV40 contaminated polio vaccines. For four decades Federal Government officials have insisted that there is no evidence that SV40 is harmful to humans or that polio vaccines produced after 1963 were contaminated with SV40. But in recent years dozens of scientific studies have found the virus in a steadily increasing number of rare brain bone and lung related tumors, the very same malignant cancers that SV40 caused in lab animals.

The subcommittee's previous hearings in September examined the intense debate raging within the scientific community between government scientists who claim that SV40 has had no effect on the human population and independent researchers from across the globe who believe SV40 is a human carcinogen.

What the government witnesses testified to at the last previous subcommittee hearing raised serious concerns about the National Cancer Institute's handling of research related to the presence of SV40 in human tumors. The subcommittee subsequently asked NCI to provide written clarification regarding several issues of concern to our investigation.

Today we have invited representatives from the NCI to reappear before the subcommittee in the hope that they might better explain and clarify the apparent inconsistencies in the research being supported by the NCI's Division of Cancer Epidemiology and Genetics

regarding the relationship of SV40 to contaminated polio vaccines. In September we also heard from Mr. Stanley Kops, a Philadelphia based attorney, regarding allegations that at least one polio vaccine manufacturer may have knowingly shipped contaminated vaccine lots after the FDA's 1961 SV40 screening regime was implemented and that not only did said manufacturer not submit vaccine safety tests to the FDA as required, but the FDA regulators failed to hold the manufacturer responsible for their failure to comply.

In response to these allegations, the subcommittee has invited representatives from the FDA and several vaccine manufacturers to present evidence that supports compliance with safe manufacturing protocols and the assertion that all polio vaccines have been, are and will continue to be SV40 free. Regrettably none of the vaccine manufacturing companies chose to attend today's hearing. And because of the mandatory nature and risk associated with all human vaccines, government health agencies have a special duty to exercise the utmost care and the approval, administration and post-administration surveillance of vaccines.

The government must always err on the side of caution in this worthy public health endeavor and to do anything less is a breach of the public trust.

This subcommittee will continue to pursue the historic truth in this matter to either reaffirm or, if necessary, rebuild the public's confidence in vaccines specifically and our public health service in general.

I look forward to hearing from our witnesses this afternoon. I think my colleague might have some quick questions she might like to submit for the record. She is in California because we are in recess.

[The prepared statement of Hon. Dan Burton follows:]

Opening Statement
Chairman Dan Burton
Government Reform Committee
Subcommittee on Human Rights & Wellness
November 13, 2003

"Preventing Another SV40 Tragedy: Are Today's Vaccine Safety Protocols Effective?"

Today, the Subcommittee is holding the second in a series of hearings examining the aftermath of the tragedy of SV-40 contamination of America's poliovirus vaccine supply in the 1950s and early 1960s.

During the first half of the twentieth century, polio stuck down hundreds of thousands of people, leaving many paralyzed – some in iron lung machines – and killing many thousands of others. The worst year for the disease in the United States was 1952, when more than 57,000 polio cases were reported, and at least three thousand of those individuals perished.

Following licensure of the Salk (inactivated) polio vaccine in 1955, the incidence of the disease fell dramatically. The disease was further reduced by the advent of the Sabin (oral) polio vaccine in 1961. In fact, the last cases of paralytic polio from natural poliovirus in the U.S. were in 1979, and the most recent case from outside the U.S. occurred in 1993.

Today, polio has virtually been eliminated from the U.S. and the entire Western Hemisphere, although it remains a threat in some developing countries.

There can be little doubt that the invention of vaccine immunization to protect children and adults from infectious diseases, as demonstrated by the success of the anti-polio campaign, was one of the greatest public health achievements of the twentieth century.

In fact, immunization as a tool against disease has been so successful that it has now become almost commonplace to use it against even relatively minor disease such as human influenza.

As a society, we have become so confident in the power of vaccines that we have even created government mandates requiring vaccinations be administered before admitting individuals to day care, public schools, college or the military.

But, what we perhaps tend to forget, is that immunization is very different than administering a medicine to combat an active illness in a person. Instead of curing a disease, vaccines instead introduce a potentially disease-causing agent into an otherwise healthy body in order to stimulate an immune response. Thus there are always risks associated with taking any vaccine. In some cases, vaccines have even been known to cause the very disease they were created to prevent.

But the risks can be greater still.

In the earliest days of polio vaccine production, laboratory tests were not sophisticated enough to detect the presence of what became known as Simian Virus 40, or SV-40. At least 26 other simian contaminants were detected and eliminated, but SV-40 slipped past quality control testing procedures and into the vaccine pool, potentially infecting millions of Americans. Soon after its discovery, scientists also learned that SV-40 could cause cancerous tumors in hamsters.

So, in society's zeal to combat one disease we as a society potentially risked exposing millions of Americans to another deadly disease. As the Subcommittee learned at our last SV-40/Polio Hearing on September 10th, we are still trying to uncover the true health impact of the SV-40 contaminated polio vaccines.

For four decades, Federal government officials have insisted that there is no evidence that SV-40 is harmful to humans, or that polio vaccines produced after 1963 were contaminated with SV-40. But, in recent years, dozens of scientific studies have found the virus in a steadily increasing number of rare brain, bone and lung-related tumors – the very same malignant cancers that SV-40 causes in lab animals.

The Subcommittee's previous Hearing in September examined the intense debate raging within the scientific community between government scientists who claim that SV-40 has had no effect on the human population, and independent researchers from across the globe who believe SV-40 IS a human carcinogen.

What the government witnesses testified to at that previous Subcommittee Hearing raised serious concerns about the National Cancer Institute's (NCI) handling of research related to the presence of SV-40 in human tumors. The Subcommittee subsequently asked NCI to provide written clarification regarding several issues of concern to our investigation. Today we have invited representatives from the NCI to reappear before the Subcommittee in the hope that they might better explain and clarify the apparent inconsistencies in the research being supported by the NCI's Division of Cancer Epidemiology and Genetics regarding the relationship of SV-40 to contaminated polio vaccines.

In September, we also heard from Mr. Stanley Kops, a Philadelphia-based attorney, regarding allegations that at least one polio vaccine manufacturer may have knowingly shipped contaminated vaccine lots after the FDA's 1961 SV-40 screening regime was implemented, and that not only did said manufacturer not submit vaccine safety tests to the FDA as required, but that the FDA regulators failed to hold the manufacturer responsible for their failure to comply.

In response to these allegations, the Subcommittee has invited representatives from the FDA and several vaccine manufacturers to present evidence that supports compliance with safe manufacturing protocols, and the assertion that all polio vaccines have been, are and will continue to be SV-40 free. Regrettably, none of the vaccine manufacturing companies chose to attend today's hearing.

Because of the mandatory nature and the risks associated with all human vaccines, government health agencies have a special duty to exercise the utmost care in the approval, administration, and post-administration surveillance of vaccines.

The government must always err on the side of caution in this worthy public health endeavor. To do anything less is a breach of the public trust.

This Subcommittee will continue to pursue the historic truth in this matter to either reaffirm or, if necessary, rebuild the public's confidence in vaccines specifically and our Public Health Service in general.

I look forward to hearing from our witnesses this afternoon.

November 10, 2003

TO: Members of the Subcommittee on Human Rights and Wellness
House Committee on Government Reform

FROM: Dan Burton, Chairman

SUBJECT: Subcommittee Hearing, entitled: "Preventing Another SV40 Tragedy: Are Today's Vaccine Safety Protocols Effective?"

The Subcommittee on Human Rights and Wellness will hold an oversight hearing on **Thursday, November 13, 2003, in Room 2154 of the Rayburn House Office Building at 2:00 p.m.**

BACKGROUND

This hearing is a follow-up to the Subcommittee's hearing of September 10, 2003 entitled "The SV-40 Virus: Has Tainted Polio Vaccine Caused an Increase in Cancer?" The development of the Salk Polio Vaccine in 1955 and the Sabin Polio Vaccine in 1962 were hailed as medical miracles by a world weary of the devastating toll of death, disability, and suffering caused by polio. During the first half of the 20th century, polio struck down hundreds of thousands of people, leaving many paralyzed – some in iron lung machines – and killing many thousands of others. The worst year was 1952, when more than 57,000 polio cases were reported in the United States. Three thousand died.

After the discovery of the Salk vaccine in 1955, mass vaccinations against polio were quickly undertaken. In the United States it is estimated that by 1961, 90% of all persons under 20 years of age and 60% of those 20 to 39 years of age had received at least one inoculation.

Polio vaccine is routinely grown on monkey kidney tissue, and the initial tissue cultures used to produce the polio vaccine came from the kidneys of rhesus and cynomolgus macaque monkeys, about 60% of which are infected with Simian Virus 40 (SV-40). Unfortunately, in the earliest days of polio vaccine production, laboratory tests were not sophisticated enough to detect the presence of SV-40. At least 26 other simian contaminants were detected and eliminated, but SV-40 slipped past the quality control testing procedures and into the vaccine pool. Soon after scientists first discovered the existence of SV-40 in 1960, they also discovered that SV-40 produces cancer in hamsters. When reports first surfaced that SV-40 could cause cancerous tumors, the United States government, starting in 1961, instituted a screening program requiring that all new lots of polio vaccine be free of SV-40 because of concerns about possible adverse effects on human health. However, already produced and contaminated vaccines were never removed from the market, and they continued to be used until as late as 1963.

There is no dispute that millions of Americans received contaminated polio vaccines that contained SV-40. And there is no dispute that SV-40 is capable of causing cancer. The disputes are: 1) how many Americans actually received the tainted vaccine; and 2) when did the Federal government truly take concrete steps to eliminate the problem.

For four decades, Federal government officials have insisted that there is no evidence that SV-40 is harmful to humans, or that polio vaccines produced after 1963 were contaminated with SV-40. But, in recent years, dozens of scientific studies have found the virus in a steadily increasing number of rare brain, bone and lung-related tumors – the same malignant cancers that SV-40 causes in lab animals.

The Subcommittee's previous hearing in September examined the intense debate raging within the scientific community between government scientists who claim that SV-40 has had no effect on the human population, and researchers from across the globe who believe SV-40 is a human carcinogen. What the Subcommittee learned at that hearing raised serious concerns about the National Cancer Institute's (NCI) handling of research related to the presence of SV-40 in human tumors. The Subcommittee asked NCI to provide written clarification regarding several issues of concern to the Subcommittee. The Subcommittee has invited representatives from the NCI to reappear before the Subcommittee in the hope that they might better explain the inconsistencies in the research being supported by the NCI's Division of Cancer Epidemiology and Genetics regarding the relationship of SV-40 to contaminated polio vaccines.

The Subcommittee also heard testimony in September from Mr. Stanley Kops, a Philadelphia attorney, regarding allegations that at least one polio vaccine manufacturer may have knowingly shipped contaminated vaccine after the FDA's 1961 screening regime was implemented, and that not only did said manufacturer not submit vaccine safety tests to the FDA as required, but that the FDA regulators failed to hold the manufacturer responsible for their failure. In response to these allegations, the Subcommittee has invited representatives from the FDA and the vaccine manufacturers to present evidence that supports compliance with safe manufacturing protocols, and the assertion that all polio vaccines have been, are and will continue to be SV-40 free.

Immunization to protect children and adults from infectious diseases has been one of the greatest public health advances of the 20th century. Government mandates require vaccinations be administered before admitting individuals to day care, school, college or the military. But vaccinations are very different than administering a medicine to combat an active illness in a person; they instead introduce a potentially disease-causing agent into an otherwise healthy body. Because of these factors, government has a special duty to exercise the utmost care in the approval, administration, and post-administration surveillance of vaccines; and the government must always err on the side of caution in this worthy public health endeavor. To do anything less is a breach of the public trust.

The Subcommittee will continue to pursue the historic truth in this matter to either reaffirm or, if necessary, rebuild the public's confidence in vaccines specifically and our Public Health Service in general.

WITNESSES:

Panel One:

Dr. William Egan
Acting Director for the Office of Vaccines Research and Review
U.S. Food and Drug Administration

Dr. Robert Hoover
Director, Epidemiology and Biostatistics Program
Division of Cancer Epidemiology and Genetics
National Cancer Institute

Panel Two:

Representative, Wyeth-Lederle Pharmaceuticals -Invited
Representative, Merck & Co. - Invited
Representative, Aventis Pasteur - Invited

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Mr. BURTON. We have the chairman of the full committee with us. Do you have any questions?

Mr. TOM DAVIS. No comments.

Mr. BURTON. No comments? Thank you.

With that, would the witnesses please stand and be sworn?

Our witnesses today for the record are Dr. William Egan, Acting Director of the Office of Vaccines Research and Review, U.S. Food and Drug Administration; Dr. Robert Hoover, Director of Epidemiology and Biostatistics Program from the Division of Cancer Epidemiology and Genetics at the National Cancer Institute. And our other panel I think did not respond. So we will continue to ask them to be here. And hopefully we will get them here in the future.

[Witnesses sworn.]

Mr. BURTON. Dr. Egan, do you or any of your colleagues have an opening statement?

Mr. EGAN. I do, sir.

Mr. BURTON. OK, Dr. Egan, proceed.

STATEMENTS OF DR. WILLIAM EGAN, ACTING DIRECTOR, OFFICE OF VACCINES RESEARCH AND REVIEW, U.S. FOOD AND DRUG ADMINISTRATION; AND DR. ROBERT HOOVER, DIRECTOR, EPIDEMIOLOGY AND GENETICS, NATIONAL CANCER INSTITUTE, ACCOMPANIED BY DR. MAY WONG, PROGRAM DIRECTOR, DIVISION OF CANCER BIOLOGY, NATIONAL CANCER INSTITUTE

Mr. EGAN. Thank you, Mr. Chairman and members of the committee. I am William Egan, Acting Director of Vaccines Research and Review at FDA's Center for Biological Evaluation and Research. Thank you for the opportunity to testify today.

The availability of vaccines has been one of the most significant public health achievements of the 20th century. Many of us can recall the devastation caused by diseases such as polio in a time when children survived in iron lungs or walked only with the help of leg braces and crutches. The polio vaccine and other childhood vaccines have likely saved more lives and prevented more illnesses than any other medical intervention.

Unfortunately, a significant number of the early poliovirus vaccine lots were contaminated with a previously unknown viral agent designated Simian Virus 40 [SV40]. A tissue culture procedure to detect SV40 was developed and officials at the Public Health Service's Division of Biological Standards notified poliovirus vaccine manufacturers that vaccine lots would be released for distribution only if test results for SV40 were negative. This requirement was also codified in Federal regulations.

Nevertheless, before SV40 was recognized as a problem and tests were in place, millions were vaccinated with poliovirus vaccines that contained SV40. Since this unfortunate event 4 decades ago FDA has required that manufacturers perform routine testing for poliovirus vaccines to demonstrate the absence of SV40.

Studies in the 1960's showed that SV40 could produce certain cancers in newborn hamsters. More recent studies reported finding SV40 genes in several types of human tumors. A report by the Institute of Medicine, which reviewed this area last year, concluded,

"The evidence is inadequate to accept or reject the causal relationship between SV40 containing polio vaccines and cancers."

For several reasons, including: Because some researchers questioned whether the tissue culture tests are sufficiently sensitive to detect low levels of SV40. FDA researchers developed a highly sensitive test based on the preliminary chain reaction technology, or PCR technology, to probe for the presence of SV40 DNA. When a random sample of oral polio vaccines manufactured between 1972 and 1996 were tested by this PCR technology, no SV40 DNA was found in any of the 30 vaccine model pools or 30 trivalent vaccine samples that were tested. FDA published these results in 2000.

Like all vaccines, the poliovirus vaccine must meet stringent standards for safety and effectiveness. Vaccines are different from most drugs in several respects, and achieving the highest quality and manufacturing is especially challenging and critical.

First, vaccines are often produced from or use living cells and organisms as well as complex growth materials derived from living sources. Thus, the potential for contamination is higher than for most drugs, and quality and purity is carefully monitored.

Second, the production of most vaccines requires growing and purifying the immunizing agents from living cells. Growth conditions are complex and subtle changes in materials in the process itself, in temperature or other conditions can affect vaccine safety, effectiveness or both.

Third, in light of these differences, we utilize the mechanism of lot release review to monitor the quality and potency of the final vaccine before manufacturers can distribute their product.

Finally, unlike most drugs, which are provided to people to treat an existing illness, most vaccines are administered to large numbers of healthy people to prevent infectious disease. Therefore, even very rare adverse events are a concern and generally are not viewed as acceptable if they can be prevented.

With this in mind, FDA's efforts to ensure safety and effectiveness begin early in the pre-approval process and continue throughout the post-approval process. As a part of this process manufacturers must meet the standards established in FDA regulations, including current good manufacturing practices [CGMPs].

FDA also uses inspection and surveillance both before and after granting a license to help assure conformity with current good manufacturing practices and standards in the manufacturer's license. Once we license a vaccine, the agency continues to monitor product safety and effectiveness.

FDA may also perform targeted inspections when, for example, there are changes to the manufacturing process, facility or equipment or other significant events.

Finally, when safety concerns arise FDA promptly responds to address these concerns.

In closing, Mr. Chairman, although scientists have not reached consensus on the potential risks posed by SV40 and whether it may

contribute to causing some types of tumors in humans, the one thing we all agree on is that poliovirus vaccine has provided an enormous public health benefit and has practically eradicated this horrible disease.

I am happy to answer your questions. Thank you.

[The prepared statement of Mr. Egan follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

STATEMENT OF

WILLIAM EGAN, Ph.D.

ACTING DIRECTOR

OFFICE OF VACCINE RESEARCH AND REVIEW

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON WELLNESS AHD HUMAN RIGHTS

COMMITTEE ON GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

NOVEMBER 13, 2003

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am William Egan, Acting Director, Office of Vaccine Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration (FDA or the Agency). OVRR regulates the development and licensing of vaccines. We appreciate the opportunity to participate in this hearing regarding Simian Virus 40 (SV40) and polio vaccine.

One of the most significant public health achievements of the 20th century has been the availability of vaccines to immunize the American public against a variety of diseases. It is important to remember how far we have come and how many vaccine-preventable diseases have been significantly reduced or eradicated in the United States. Many of us can recall the devastation caused by diseases such as polio; a time when children survived in iron lungs or walked only with the help of leg braces and crutches. The polio vaccine and other childhood vaccines can be credited with saving more lives and preventing more illnesses than any other medical intervention. While vaccines are generally very safe and effective, FDA is committed to continuing to monitor and, wherever possible, improve their safety. Therefore, we share your committee's concerns about assuring vaccine safety and appreciate the opportunity to comment on the potential risk from SV40, a risk that has been eliminated from U. S.-licensed vaccines.

BACKGROUND

In the early 1900s, Americans were frightened of polio and with good reason. Polio is a highly contagious disease that paralyzes or kills its victims and children are especially vulnerable. During the early 1950s, Dr. Jonas Salk developed a killed-virus polio vaccine. After large scale testing in 1955, the Salk polio vaccine became an important immunization tool when four million doses of the vaccine were manufactured and distributed.

In the late 1950s, Albert Sabin theorized that a weakened, live-virus polio vaccine would provide longer-lasting immunity. By the end of the 1960s, the vaccine developed by Sabin, which was administered orally, became the primary weapon for polio prevention in the U.S. The widespread use of polio vaccines throughout the world – primarily oral poliovirus vaccine (OPV) – has led to the eradication of wild-type polio in the Americas and the near eradication of polio worldwide. Although highly effective, the Sabin vaccine is an attenuated form of the poliovirus that can mutate. Vaccine recipients can, in rare cases, develop polio after taking this vaccine. In the U.S., there were approximately 6-8 cases per year of vaccine-associated paralytic polio (VAPP). Because the risk of VAPP exceeded the risk of disease from wild-type polio, the Salk inactivated vaccine became the only product recommended and used for routine childhood vaccination in the U.S. in 2000.

SIMIAN VIRUS 40

The inactivated Salk vaccine was not without problems. Where problems were identified, however, the science community quickly responded to improve the safety of the vaccine.

A significant number of early vaccine lots were contaminated with the previously unknown viral agent, SV40. In 1960, Drs. Sweet and Hilleman identified SV40 in monkey kidney cells and seed stocks used to produce the poliovirus. In 1961, Drs. Gerber, Hottle, and Grubbs discovered that the treatment used to inactivate SV40 was not completely effective.

In response to these problems, scientists, including those at the Public Health Service's (PHS) Division of Biological Standards (DBS), developed a tissue culture procedure to detect SV40. Once this procedure was developed, DBS notified manufacturers that " . . . no lots of poliomyelitis vaccine will be released in the absence of negative results of a valid tissue culture test for SV40." This requirement was later codified in regulations. Nevertheless, before SV40 was recognized as a problem and appropriate tests were developed, millions of people were vaccinated with poliovirus vaccines that contained SV40. Since this unfortunate event four decades ago, FDA has required that manufactures perform routine testing for oral poliovirus vaccines to demonstrate the absence of SV40.

Studies in the 1960s showed that SV40 could produce certain cancers in newborn hamsters. More recent studies reported finding SV40 genes in several types of human tumors. These findings have raised the question of whether SV40 may cause, or

contribute to causing, some types of cancer in humans. Several epidemiological studies found no link between exposure to SV40 contaminated vaccines and development of cancer. However, a study of immunization of pregnant women showed an increase in certain cancers in the offspring of women immunized with IPV compared to women immunized with either OPV or influenza vaccine. However, a recent report by the Institute of Medicine of the National Academy of Sciences concluded that "the evidence is inadequate to accept or reject a causal relationship between SV40 containing polio vaccines and cancer."

Recent studies have reported finding SV40 genes in several types of human cancers. This has raised questions about the potential for various modes of SV40 transmission in the human population and the question of whether SV40 was circulating in the human population before the advent of the polio vaccines. However, other research suggests that the tissue culture tests may not be sufficiently sensitive to detect low levels of SV40 that might potentially be present in current polio vaccines. In response to this concern, FDA researchers developed a highly sensitive test based on the polymerase chain reaction technology to probe for the presence of SV40 DNA in vaccines. Random samples of live oral polio vaccines manufactured in the U.S. between 1972 and 1996 were tested using this technology. No SV40 DNA was found in any of the 30 vaccine monopools we tested. The results of this testing were published in 2000 in the peer reviewed journal, Biologicals.

ASSURING VACCINE SAFETY

Vaccines are different from most drugs in several respects and achieving the highest quality in manufacturing is especially challenging and critical. First, vaccines are most often produced from or use living cells and organisms, as well as complex growth materials derived from living sources. Thus, the potential for contamination is higher than for most drugs and, hence, the quality and purity of all source materials are carefully monitored. In fact, a separate Federal entity for regulating biological products was first established, well before FDA itself, under the Biologics Control Act of 1902 to address these concerns.

Second, the production of most preventative vaccines requires growing the immunizing agent (i.e., bacteria, viruses, etc.) in the production facility and the purification of complex molecules from these organisms. Growth conditions are complex, and subtle changes in materials, the process itself, or in conditions such as temperature can result in changes in the final vaccine that can affect its safety, its effectiveness, or both.

Third, the final vaccine is usually not, like most drugs, a simple molecule that can be tested for purity and potency using simple chemical and physical methods. Instead, each lot of vaccine must be carefully tested for composition and potency. They are also tested to ensure that they are free from contamination through the manufacturing and, where necessary, lot release process.

Finally, unlike most drugs, which are provided to people to treat an existing illness, most vaccines are administered to large numbers of healthy people to prevent infectious diseases

prospectively. For this reason, even very rare adverse effects are of concern and generally not viewed as acceptable to healthy children and adults if they can be prevented. For all of these reasons, the entire process of vaccine manufacturing is highly demanding and complex; both the licensing of vaccines and the regulation of vaccine production is subject to rigorous expectations and standards. In addition, FDA works with multiple partners to help encourage development and implementation of new and improved methods of vaccine production and improved testing that may further enhance vaccine safety.

VACCINE APPROVAL PROCESS

FDA's vaccine approval process can be divided into pre-approval and post-approval activities.

Pre-approval Activities

Early in the pre-approval process, sponsors test candidate vaccines in animals, where appropriate, to be sure they are safe and confirm that they induce appropriate protective responses against the infectious disease. They then conduct clinical trials in humans to determine appropriate dosing and to generate safety and efficacy data that can be used as a basis for approving a marketing application. For studies conducted under an investigational new drug application (IND), FDA often provides guidance on both animal studies and on clinical trial conduct and design. This guidance is intended both to protect human subjects and to assure that the studies performed are likely to help determine whether the product is safe and effective.

Current Good Manufacturing Practices

Section 351(a) of the PHS Act requires that a vaccine manufacturer demonstrate that the biological product is "safe, pure, and potent." It further requires that the "facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent." As part of these requirements, manufacturers must meet the standards established in FDA regulations applicable to biologics, including current good manufacturing practices (CGMP). CGMPs consist of the current industry practices and FDA regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). The term CGMP has its origin in the Federal Food, Drug, and Cosmetic (FD&C) Act, section 501(a)(2)(B), which states that a product is adulterated if "a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with CGMPs to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

FDA uses inspection and surveillance, both before and after licensure, to help assure conformity with CGMP and the standards set forth in the manufacturer's license. The goal is to ensure that consumers receive vaccines and other FDA-regulated products that meet requirements for safety and effectiveness. The Agency strives for consistency in its inspections, paying particular attention to serious violations, such as contamination in the production facilities and processes and looking for underlying systemic problems, such as lack of a documented and validated process, inadequate quality control, and repeated record-keeping omissions or errors.

POST APPROVAL ACTIVITIES

Once FDA licenses a vaccine, the Agency continues to monitor product safety and effectiveness. For vaccines, FDA accomplishes this through ongoing review of adverse events reported under the Vaccine Adverse Event Reporting System, through post-licensure inspections, and through other post-marketing activities. FDA performs inspections to determine whether manufacturers are applying CGMP and the standards set forth in their biologics license application. FDA may also perform targeted inspections when, for example, there are changes to the manufacturing processes, facility, or equipment, or other significant events.

Lot Release

FDA also utilizes the mechanism of lot release review to monitor the quality and potency of the final vaccine before manufacturers distribute their product. Because of the complex manufacturing process for most biological products, each lot of product undergoes appropriate testing by the manufacturer prior to release for distribution. The manufacturer performs specific tests as set forth in its license application, such as those for sterility and potency, and then submits the results to the Agency. The manufacturer also submits lot release protocols, and if applicable, product samples, before the product may be distributed. The lot release program is an essential quality check on product specifications and is part of FDA's multi-pronged strategy designed to help assure biological product quality.

CONCLUSION

Prior to 1962, poliovirus vaccines produced in rhesus monkey kidney cells were contaminated with SV40, a virus that can cause tumors in some rodents. Recent studies reporting that SV40 was detected in some human tumors raised concerns that SV40 may be pose a risk in humans. Following the recognition that SV40 could contaminate cell cultures used to produce polio vaccine and the availability of testing for SV40, FDA required specific tests to assure that poliovirus vaccines are not contaminated with SV40 virus. FDA retested samples of live oral polio vaccines manufactured in the U.S. between 1972 and 1996, and no SV40 DNA was found in any of the lots tested.

FDA's regulation of vaccine manufacturing, including its continuing activities to assure and enhance vaccine safety, is critical to maintaining public confidence in U.S. licensed vaccines. The importance of public confidence must be stressed. No other single health intervention has had the impact on disease prevention and our nation's health as immunization with U.S. licensed vaccines. For this reason, FDA carefully evaluates each licensing and regulatory action it takes, balancing the importance of product availability while working with manufacturers to help assure that products distributed to consumers are as safe as current technologies allow will.

Although scientists have not reached consensus on the potential risks posed by SV40 and whether it may contribute to causing some types of tumors in humans, the one thing we all agree on is that poliovirus vaccine has provided an enormous public health benefit and has practically eradicated this horrible disease. As with all medical products, there are potential

known and unknown risks with any vaccine. FDA will continue its efforts to help ensure the safety of all vaccines and protect the public health.

Thank you again for this opportunity to appear before you today. I am happy to answer your questions.

Mr. BURTON. Thank you, Dr. Egan.

Dr. Hoover.

Dr. HOOVER. I am Robert Hoover, a physician epidemiologist, currently Director of the Epidemiology and Biostatistics Program. Accompanying me today is my colleague, Dr. May Wong, a Program Director from NCI's Division of Biology, and we are pleased to be here, particularly since NCI has historically been and continues to be responsible for a substantial proportion of the research into the role of Simian Virus 40 in carcinogenesis.

Both my written and oral comments will be brief since NCI did submit substantial testimony last September.

For several decades the NCI has been supporting research directed at understanding SV40 carcinogenesis in several areas. Most of this support has been in the area of laboratory studies of molecular virology and carcinogenesis, and other efforts have been focused in epidemiology.

In the past decade multiple investigations from independent laboratories have identified SV40 in tumor samples, as you mentioned, from mesotheliomas, brain tumors, osteosarcomas, and non-Hodgkins lymphoma.

Some research groups have described unique characteristics of these SV40 DNA sequences and the detection of viral proteins and tumors, both of which argue against the laboratory contamination as an explanation. However, when detected, SV40 appears to be present in very low amounts, which has complicated our understanding of what this detection means. Additionally, using the same highly sensitive molecular techniques, other research groups have not detected SV40 in the same tumor types.

Recognizing some of the difficulties and limitations of current approaches, the Institute of Medicine recommended the development of and use of sensitive and specific standardized techniques for SV40 detection. Meanwhile, those who have found evidence of SV40 infection in human tumors have also begun the more difficult task of attempting to discern whether this infection actually plays a role in the development of these cancers.

The other line of scientific inquiry is provided by epidemiologic studies which examine the relationship between SV40 and exposure or infection and the risk of cancer in human populations. To date most of these studies have relied on large population-based cancer registries, such as NCI's SEER program or the Danish Cancer Registry, to examine the incidence of cancer in people who had a high probability of receiving SV40 contaminated polio vaccine as children.

Up through the 1990's these studies have failed to detect evidence of an increased risk of those cancers suggested by the molecular biology work, indicating that it is unlikely that there is an epidemic of these cancers that might be attributed to SV40 contaminated polio vaccine. Nonetheless, as pointed out by the Institute of Medicine, it has not been possible in these studies to be certain which individual persons were actually infected through receipt of contaminated vaccines.

Thus, to answer the question of whether there is any increased risk and, if so, of what magnitude of cancer from such exposure will require more epidemiologic research, using specific data on ex-

posure for individuals. Some attempts have been made to do this by testing for antibodies to SV40 and cancer cases and controls. To date these studies have not indicated an increased risk for those with such antibodies. However, because of limitations in our current technologies, these studies cannot be considered definitive. Here again the development of accurate tests for SV40 infection, in this instance serologic tests called for by the Institute of Medicine, will facilitate future epidemiologic research on the question of whether SV40 causes cancer.

In summary, we agree with the Institute of Medicine that the evidence is inadequate to accept or reject a causal relationship between SV40 containing polio vaccines and cancer. At the moment there is no consensus in the scientific community on whether SV40 causes cancer in humans. When working at the cutting edge of science this situation is neither unusual nor surprising. Different disciplines and different groups using a variety of approaches and techniques frequently come up with contrasting results. Indeed, it is in pursuing the scientific answers for such differences that our knowledge is enhanced and we are able to move the science forward.

At NCI we are committed to the support and conduct of the scientific research that will lead to the needed answers. We are particularly optimistic that improved tools for the detection of SV40 infection can be developed and thus allow the power of molecular virology to be combined with the rigor of the epidemiologic method in addressing these important questions.

And I would be happy to take your questions.

[The prepared statement of Dr. Hoover follows:]

Testimony
Before the Subcommittee on Wellness and Human Rights
Committee on Government Reform
United States House of Representatives

Statement of
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For Release on Delivery

Expected at 2:00 PM on

Thursday, November 13, 2003

Thank you, Mr. Chairman, for inviting the National Cancer Institute (NCI), an agency of the National Institutes of Health, Department of Health and Human Services, to appear before the subcommittee today. I am Robert Hoover, M.D., a physician-epidemiologist, currently the Director of the Epidemiology and Biostatistics Program of the Division of Cancer Epidemiology and Genetics (DCEG). Accompanying me today is my colleague, May Wong, Ph.D., a program director from the NCI's Division of Cancer Biology. We are pleased to be here, particularly since the NCI has historically been and continues to be responsible for a substantial proportion of the research into the role of simian virus 40 (SV40) in carcinogenesis.

Both my written and oral remarks today will be brief, since the NCI did contribute substantial testimony at the last meeting of the subcommittee on this topic in September, and we have responded to your additional questions following that hearing. Also, the Institute of Medicine (IOM) of the National Academy of Sciences recently issued a comprehensive summary and critical review of the research in this area, at the request of the National Institutes of Health and the Centers for Disease Control and Prevention.

Overview of the Research Field

SV40 was discovered initially in monkey kidney cells used as culture media to grow polio virus for the original Salk and Sabin polio vaccines. This, and the subsequent discovery that this virus had the capacity to cause multiple different tumors in rodents exposed as newborns, caused concern about what effect vaccination with contaminated polio vaccine might have had on human populations. Laboratory reports in the 1990s of

possible detection of SV40 virus in some human malignancies heightened these concerns. The NCI has been supporting research directed at understanding SV40 carcinogenesis in several areas. Most of this support has been in the area of laboratory studies of molecular virology and carcinogenesis, and other efforts have been focused in epidemiology.

Research Line of Inquiry: Molecular Virology and Carcinogenesis

In the area of molecular virology and carcinogenesis, much work by extramural scientists, funded in part by NCI, has focused on the question of (1) whether SV40 is present in some human tumors; and (2) what the biological role of this virus might be. In the past decade, multiple investigators from independent laboratories have identified SV40 DNA in tumor samples from mesotheliomas, brain tumors, osteosarcomas, and non-Hodgkin's lymphoma.

Some research groups have described unique characteristics of these SV40 DNA sequences and the detection of viral proteins in tumors, both of which argue against laboratory contamination as an explanation. However, when detected, SV40 appears to be present in very low amounts, which has complicated our understanding of what this detection means. Additionally, using the same highly sensitive molecular techniques, other research groups have not detected any SV40 in the same tumor types.

The reasons for these discrepancies are unclear. Recognizing some of the difficulties and the limitations of current approaches, the Institute of Medicine recommended the "development and use of sensitive and specific standardized techniques for SV40

detection." Those who have found evidence of SV40 infection in human tumors have also begun the more difficult task of attempting to discern whether this infection actually plays a role in the development of these cancers.

Research Line of Inquiry: Epidemiology

The other line of scientific inquiry - studying the question of whether SV40 causes human cancer - is provided by epidemiological studies, which examine the relationship between SV40 exposure or infection and the risk of cancer in human populations. Most of these studies have relied on large population-based cancer registries, such as the NCI's SEER registry program or the Danish cancer registry, to examine the incidence of cancer in people who had a high probability of receiving SV40-contamined polio vaccine as children.

Up through the 1990's, these studies have failed to detect an increased risk of those cancers suggested by the molecular virology work. The epidemiologic studies are important because, together, they indicate that it is unlikely that there is an "epidemic" of cancer that might be attributed to SV40-contaminated polio vaccine. Nonetheless, as pointed out by the Institute of Medicine, it has not been possible in these studies to be certain precisely which individual persons were actually infected with SV40 through receipt of contaminated vaccines. Thus, to answer the question of whether there is any increased risk of cancer from such exposure will require more epidemiologic research using specific data on exposure for individuals.

Some attempts have been made to do this by testing for antibodies to SV40 in cancer cases and controls. To date, these studies also have not indicated any increased risk for those with such antibodies. However, because of limitations in our current technologies, these studies cannot be considered definitive. Here again, the development of accurate tests for SV40 infection, called for by the Institute of Medicine, will facilitate future epidemiological research on the question of whether SV40 causes cancer in humans. Specifically, the Institute of Medicine report recommended "development of sensitive and specific serologic tests for SV40."

Future Research

As I have discussed, two parallel lines of research investigation – molecular virology and epidemiology – have been moving forward in an effort to answer important questions about the role of SV40 in human cancer. The scientific process of developing an hypothesis, conducting studies, publishing in peer-reviewed journals, reviewing different perspectives from the research, and then designing new investigations, is working well. With the remarkable progress we are making in understanding the molecular basis of disease, I anticipate that a clearer picture of the potential role of SV40 in human malignancy should emerge from this process. The course of future progress should also be enhanced by taking account of the research recommendations of the IOM report.

Summary

In summary, we agree with the Institute of Medicine, as stated in their report, that "the evidence is inadequate to accept or reject a causal relationship between SV40-containing polio vaccines and cancer." At the moment, there is no consensus in the scientific community on whether SV40 causes cancer in humans. When working at the cutting edge of science, this situation is neither unusual nor surprising. Different disciplines and different groups, using a variety of approaches and technologies, frequently come up with contrasting results. Indeed, it is in pursuing the scientific answers for such differences that our knowledge is enhanced and we are able to move the science forward.

Harald zur Hausen, an eminent virologist, and Editor-in-Chief of the *International Journal of Cancer*, recently summed up the situation as follows: "The truth [about whether SV40 causes cancer in humans] will hopefully come out in the future... In the meantime, it is clearly premature to label SV40 as a human carcinogen; a healthy skepticism stimulates more experiments and certainly does not harm scientific progress." At NCI, we are committed to supporting and conducting the scientific research that will lead to the answer. We are particularly optimistic that improved tools for the accurate detection of SV40 infection can be developed, and thus allow the power of molecular virology to be combined with the rigor of the epidemiologic method in addressing these important questions.

I would be pleased to answer your questions.

Mr. BURTON. Thank you very much. Dr. May Wong, do you have a comment you would like to make?

Dr. WONG. No.

Mr. BURTON. OK. Thank you. If you would like to answer—help answer these questions, we can move that mic back and forth.

We have had a number of parents before my committee over the last 4 or 5 years whose children had medulla blastoma and died, and many of those feel that SV40 could have been the culprit, could have been passed on through the parent to the child. We had one case where the father, I think, ultimately died as well of cancer. So those things are kind of heart rending. That's one of the reasons why we are very aggressive in trying to get the answers to these questions.

We also have a former employee of one of our government research agencies that provided an awful lot of information on this. I am not at liberty to give his name out right now. But as you read, I am sure, your agency as you went through the questions in our letter knew that didn't come out of my brain. And so we are very anxious to get accurate answers and I know you want to be as accurate as possible. We don't have a lot of media here today or anything, but I hope that we will be able to get as many accurate answers as possible because this is an issue that, like some of the others we have raised, is not going to go away, you know, as long as I can hold these hearings.

Dr. Hoover, you are not specifically an expert on SV40, is that correct?

Dr. HOOVER. That is correct.

Mr. BURTON. What is your area of expertise?

Dr. HOOVER. Epidemiologic methods. I've studied a variety of tumors and exposures over my career, applying the epidemiologic method to that.

Mr. BURTON. You're familiar with the subcommittee's recent exchange and correspondence with the NCI regarding the SV40 research, is that correct?

Dr. HOOVER. Yes, I am.

Mr. BURTON. Do you have any idea why the National Cancer Institute did not send somebody who has expertise in SV40?

Dr. HOOVER. Well, I'm responsible for the program that does viral epidemiology. I'm the program director and that branch is under my direction, so——

Mr. BURTON. Yes, sir. Do you have under your jurisdiction people who have expertise in SV40?

Dr. HOOVER. Correct.

Mr. BURTON. Why didn't we have one of those come as well?

Dr. HOOVER. We sent one last time when it looked like you were asking for a more global view, or whatever, of the science.

Mr. BURTON. Well, we may want to ask them to come back in the future if we don't get, you know, all the questions answered.

In its November 7, 2003 response to this subcommittee the National Cancer Institute claims that the NCI fact sheet on SV40 presents a balanced view of the current research surrounding the connection between SV40 and human cancer. For example, the NCI fact sheet states that the Institute of Medicine issued a report in October 2002 which concluded that the scientific evidence was in-

sufficient, I think you mentioned that today, to prove or disprove the theory that exposure to poliovirus vaccine contaminated with SV40 resulted in cancer in humans. As I said, I think you stated that a while ago.

Do you agree that the fact sheet represents or presents a balanced view of the current research surrounding the connection between SV40 and human cancer?

Dr. HOOVER. Well, we thought that since it gave evidence and pointed out the conflicts and the only conclusion reached didn't reach its own independent conclusion—the only conclusion reached was the Institute of Medicine's conclusion with a link to the Institute of Medicine's Web site—we thought it was reasonably balanced, but as Dr. Von Eschenbach wrote to you and as you're probably aware from the controversy over our fact sheet on abortion and breast cancer in the past year, whenever anyone asks us to review a fact sheet, any responsible body or person, we do it, and Dr. Von Eschenbach has asked that fact sheet be reviewed for its balance.

Mr. BURTON. So what you're saying is that you think it is a balanced view?

Dr. HOOVER. I thought it was a reasonable view, but it could stand to be reviewed again.

Mr. BURTON. The NCI fact sheet was last reviewed in April 2003, well after the IOM report was issued in October 2002. That's correct, isn't it?

Dr. HOOVER. That's correct.

Mr. BURTON. Is it true that the IOM report concluded that the scientific evidence was inadequate to prove or disprove the theory because the epidemiological studies like those conducted by the NCI were too flawed to be scientifically useful?

Dr. HOOVER. That was part of their—the reason for their conclusion, yes.

Mr. BURTON. Is it true that the IOM report concludes that the biological evidence is strong that SV40 is a transforming or cancer causing virus?

Dr. HOOVER. That is correct.

Mr. BURTON. Is it true that the IOM report concludes that the biological evidence is of moderate strength that SV40 exposure could lead to cancer in humans under natural conditions?

Dr. HOOVER. That is correct.

Mr. BURTON. Is it true that the IOM report concludes that the biological evidence is of moderate strength that SV40 exposure from the polio vaccines is related to SV40 infection in humans?

Dr. HOOVER. That is correct.

Mr. BURTON. Why does the NCI Web site omit these conclusions from its discussion of the IOM report?

Dr. HOOVER. The Web site is intended to give information to the general public about issues concerning cancer, and the bottom line issue in SV40 is does it cause cancer in human populations. And the bottom line conclusion of the Institute of Medicine's report was it is unknown at this point, the science is not adequate to either rule it in or rule it out. And that was what we tried to convey and presented some of the contrasting information on either side. We

did also provide a link to the IOM site itself on our site so that people could go directly to it.

Mr. BURTON. The American people would like to have, especially in the Internet age, as much information as possible when they're talking about vaccinations of their children and themselves, and so you omit this from your Web site. And we had a similar answer from the NCI, not the NCI but the FDA, on whether or not the mercury in the vaccinations which has a cumulative effect in the body, in the brain, could cause neurological problems such as autism in children and possibly contributed to Alzheimer's in adults. And I can't understand why they don't put on the Web sites, you know, that this is one of the things that has not been proven or disproven so that people can at least have that information that there's a possibility that cancer is caused by SV40, and that there's a possibility, very strong, and from scientists around the world, on these vaccinations that I talked about from FDA that contain mercury that they could cause neurological problems. And I can't understand why we don't put on the Web sites that kind of information.

Dr. HOOVER. Well, I think we did try to indicate that there is the possibility they could cause cancer. That was the whole reason for the Web site and the presentation of some of the evidence that has been produced to raise that question and included the conclusion of the IOM report which indicated that it couldn't rule it out, and also the link to the IOM Web site for those who wanted more detailed information so they could click and go there.

But as I mentioned, we review these all the time when someone thinks that they don't reflect the appropriate balance or the appropriate summary, and we will review them and I will certainly include in that your recommendation that the other conclusions of the IOM report be considered for inclusion.

Mr. BURTON. Thank you. I appreciate that. You know, in the questions you answered just a minute ago, those epidemiological studies that were conducted by NCI, according to the IOM report, were too flawed to be scientifically useful and you said that's true, that is what the IOM report——

Dr. HOOVER. Too flawed to be scientifically useful to determine whether or not SV40 causes cancer in humans or not. They are useful, those kinds of studies are useful to frame the risk, if there is one. And that's why I mentioned in my written and my oral testimony that it—by not seeing any impact on the rates in the general population among those age groups that were most likely to have received the contaminated vaccine does rule out an epidemic, the classic ones we have seen for tobacco related diseases, estrogen and endometrial cancer, AIDS, AIDS virus and Kaposi's sarcoma. All of those show up because they are so widespread and they are so strong. They all show up pretty readily in these kinds of epidemiologic investigations. So we didn't see that.

It does not, however, give you the kind of power that other kinds of epidemiology do, when you can actually identify people who have been infected and people who haven't and look at their cancer experience or look at people who have cancer and evidence of infection in them and people that don't. Those are so-called analytic epidemiologic studies, much more powerful. Those are the ones that

people use to support or not support carcinogenesis for a particular agent. Those actually, we agree with the Institute of Medicine, those can't be done to the best of our abilities at this point because the measurement techniques are not good enough to do that, to validly identify everybody who got infected and those that didn't. But we actually are, as I mentioned, very enthusiastic that with modern molecular technology and all of the research that's going on that we will actually get those tools in the very near future and be able to do something about it.

Mr. BURTON. That's good. The epidemic of various forms of cancer that we see in the United States would lead one to believe that there's some major causes and since SV40 was shown to be a carcinogenic in laboratory hamsters, it seems that you'd want to make sure that people had some idea. I'm not concerned so much about the liability that the pharmaceutical companies might have unknowingly incurred because we protect them legislatively in most cases. But the American people I just think need as much information as possible so that they can deal with these problems.

Dr. HOOVER. I agree.

Mr. BURTON. You know I've had people before the committee who almost blame themselves for their children's brain cancers or their wife's breast cancer. And of course my wife, as you know, died from cancers. And it would mentally relieve them of some of this if they thought that there was a cause that you could point to.

Dr. HOOVER. I agree with you thoroughly, and I believe that we need to focus on identifying causes and we need to focus on this particular one. When I have been taking care of patients, the most difficult time I had was dealing with children who had cancer. Children aren't supposed to get cancers, and there's no more driving force in my life than those observations and those feelings to try and identify causes of cancer.

Mr. BURTON. Well, I appreciate that and I do hope that we will be able to get more information on the Web sites.

Also from the November 7, 2003 response to the subcommittee, NCI states that in light of a body of evidence which demonstrates that there may be some SV40 in some rare human tumors, NCI will review the fact sheet. Is that an admission by NCI that SV40 is in fact present in human tumors?

Dr. HOOVER. There is certainly a large body of evidence out there indicating that it is.

Mr. BURTON. Well, if so, what evidence has come to light since April that convinced the NCI of that fact?

Dr. HOOVER. I think NCI has always been convinced that there's a large body of evidence and certainly growing all the time that there is SV40. We support most of that research actually and—of the people who have identified it. There are problems interpreting it because we get this wide range of estimates from 3 percent to 90 percent and not everybody that looks for it can find it. But those are probably not to be unexpected in using new technologies and sort of working, as I mentioned, working at the cutting edge. I think we can, with time and with more people getting involved in the field, sort out those issues and those concerns.

Mr. BURTON. What explanation or theory does the NCI offer for SV40 being present in human tumors? I mean, how did it get in these tumors?

Dr. HOOVER. That's a very good question, and I don't think we know. The only relevant exposures that we know of or the only exposures we know of happening in this population has been through contaminated vaccine. There are places in the world where people have pretty close contact with the monkeys that are infected with the virus, so perhaps in those locales they can get it in an epizootic kind of sense. But——

Mr. BURTON. Here in the United States we don't have a lot of people coming in contact with monkeys.

Dr. HOOVER. No, we don't. If there are, I think as the Institute of Medicine pointed out, once the techniques for measurement get better, they actually think one of the first things we should do is go back to tumors that occurred in the 40's and early 50's and test them to see if there's evidence of SV40 in them.

Mr. BURTON. Before the vaccines were used.

Dr. HOOVER. Before the vaccines.

Mr. BURTON. Well, was the SV40—was monkey tissue used in other vaccines?

Dr. HOOVER. Not that I know of. This was their attempt to see——

Mr. BURTON. OK. Was SV40 found in other areas other than the monkeys and the vaccine that came from the monkey tissues?

Dr. HOOVER. Right now the only host that I know of—I'm not an expert in this area—is the monkeys. But we don't—there's a lot we don't know about infectious diseases and whether there might be another source of SV40 infection out there that we don't know about now I think is what the Institute of Medicine was concerned that aspect be pursued too, that perhaps this virus or a very, very highly related virus molecularly may actually come from somewhere else as well.

Mr. BURTON. Come on. You don't believe that. I mean, you're a very—I'm sure you're a very dedicated scientist and doctor. But if it's only in the monkey and the monkey tissue is used to make the vaccine and you know of no other place that SV40 comes from and people in the United States have SV40 and cancerous tumors, deductive reasoning would lead you to believe that it came from the vaccination unless somebody's got a bunch of monkeys running around their house.

Dr. HOOVER. That seems to be the most likely explanation. But we also agreed with the Institute of Medicine report that indicated that we should make sure of that by looking at tissues from people who couldn't have been exposed to that—by that route to see whether I agree with that.

Mr. BURTON. So there really is no explanation from the NCI on SV40 being in humans?

Dr. HOOVER. Other than from contaminated polio vaccines and in other parts of the world the contact with monkeys, no, we don't have another.

Mr. BURTON. Well, you know as bright as everybody is over there I would think that they'd come to the conclusion before going back

to pre-1950 vaccinations and other things that the SV40 was the culprit. But——

Dr. HOOVER. Me personally, and a lot of us, have been burned too many times by thinking we know something without the data to prove it and so we are generally in the business of going out and finding the data to demonstrate that. And I think that's what the Institute of Medicine wanted to do.

Mr. BURTON. Well, parents of kids who died from medulla blastoma, I think would like to know if there's a strong possibility that the SV40 was the cause. And if there's no other avenue that we know of, I think the parents should at least have that kind of information. It would allay some of the pain that they've gone through. I mean, you know, to say well, we don't know, when you know the only source that's known to man is the monkey and the virus that was in the—and the polio vaccine, to just keep saying we don't know, I think is—I think maybe you should reframe that and say it's probable, it's probable that the vaccine caused it. You've got an out there. But——

Dr. HOOVER. Well, I think it's probable that SV40 contamination of vaccine is responsible for infection in the U.S. population. The significance of the SV40 in the tumors has yet to be determined and I'm sure all the molecular scientists who are working night and day on that issue, the issue of is that because they get to find the virus in the tumors is the virus related to that tumor, that's another question and that is the hardest question of all to answer.

Mr. BURTON. You know, I would think there would be a major, major scientific research project.

Dr. HOOVER. It is.

Mr. BURTON. Well, I hope so, because my gosh, all the people that are dying of cancer, my wife, people who are suffering from breast cancer, medulla blastoma, all these people, all these various kinds of cancer that 25 years ago you never saw or very rarely saw, you'd think that if you thought the culprit might be SV40 that all hell would break loose to get the research done so that we might stop it in the future if we can or find a cure that might negate SV40 from killing somebody.

Dr. HOOVER. I think that's why, I know, Dr. Wong's program is funding probably about $9 million worth of research a year in SV40 molecular virology.

Mr. BURTON. Nine million?

Dr. HOOVER. Yes.

Mr. BURTON. How much money does our health agency get over there? NCI, how much do you get over there?

Dr. HOOVER. You'll have to tell me. I know what our own budget is. Several billion.

Mr. BURTON. Several billion?

Dr. HOOVER. Right.

Mr. BURTON. Several billion, and the culprit for cancer in many cases may be SV40 and you're dedicating $9 million to this project?

Dr. HOOVER. There are very many candidates for what may cause cancer in human population, an extremely large number, and we try to keep a balanced portfolio to investigate everything for which there is a likelihood.

Mr. BURTON. I know, Dr. Hoover, but here you know probably this is, and very strongly possibly, this could be a culprit because you've found it in cancerous tumors in human beings and it seems to me that you know it was in laboratory animals. You know it's showing up in human cancers. It seems that this would be a top priority and would get more money than $9 million out of a multi-billion dollar appropriation.

Dr. HOOVER. Well, I'm not the one that makes those decisions, but the people who send in grants do. One of the problems in making headway in any area where you think you have something that's worth investigating is do you have the tools available to you to make—to get the answer. And that's what the grant mechanism is supposed to determine when people send in grants and tell their ideas to the study section. People decide, OK, who's got the best tools to answer this question? I think we need better tools in the area of viral carcinogens.

Mr. BURTON. Could I ask your associate, Dr. May Wong, a question?

Dr. HOOVER. Sure.

Mr. BURTON. And this may put you on the spot. Put the mic real close to you. This may put you on the spot and I don't want to do that. I mean we're here today not to beat up on anybody. I have been accused of that in the past. I see you smiling a little bit there. What we want to do is get the facts out and try to do something constructive about the possible cause of cancer.

Would additional funding be helpful?

Dr. WONG. Yeah. I really agree with you. I think we do need additional research funds. Unfortunately, I guess under the current fiscal environment, you know, we're obligated with so many different areas of research not just on SV40, but other things, but in terms of SV40, yes, I do agree, I think maybe you or the Congress can set aside or appropriate, you know.

Mr. BURTON. You mean dedicate a certain amount of money?

Dr. WONG. Dedicate a certain amount of funds.

Mr. BURTON. How much money do you think—and I know this is a tough one. How much money do you think would be necessary to do—you don't want to do overkill, but an adequate job of investigating this?

Dr. WONG. No. No. We have been really actually thinking about this problem quite a long time and I think what is also lacking is that cross-discipline area, you know, the collaborations between, like, from our part is mostly the molecular virologists, molecular biologists. We need to really collaborate and work with other parts of disciplines such as epidemiologists. Currently that's not being really done. That's why we have a lot of confusion in the area.

Mr. BURTON. Well, what I would like to have from you——

Dr. WONG. Is a dollar figure?

Mr. BURTON. No, no, not just a dollar figure. And Dr. Hoover, could you give this subcommittee a recommendation on how you could come to a conclusion, if possible, quicker? I mean, she's saying that there needs to be a cross-pollination between researchers in order to find out, you know, if this is a culprit and ultimately lead to maybe some kind of a cure or, like AIDS, maybe a way to prolong life without stopping the AIDS. You see what I mean? And

if we could get from you some kind of a statement that would say—tell us how that cross-pollination should take place, in addition to, and in the letter, or recommendation, in addition to the amount of money you think is necessary for additional research, I would be very happy to go to the appropriators and to the authorizing committees and write a letter directly to your superiors at the agency saying this is what our subcommittee found should be done. I don't want to jeopardize you by going to your superiors and saying, hey, you guys aren't doing your job and here's what's recommended, but I think it would be helpful if we in Congress knew what your recommendation is so we could convey that to the authorizers, appropriators and the people at the top of the agencies. Could you do that for us?

Dr. WONG. Yeah, I think we can go back and discuss amongst each other, you know, what is the best approach and then get back with you.

Mr. BURTON. We'd like to do that because then maybe we can help you get that approach. We'd like to do that. OK.

What explanation or theory does the NCI offer for SV40—well, you've already answered that question. You don't really have an answer yet, although you think it's likely that it's from the SV40.

Who are the experts who will review this fact sheet for accuracy and balance?

Dr. HOOVER. That's up to Dr. von Eschenbach. The fact sheets are run out of his office, and it's done in different ways for different times. For the abortion and breast cancer fact sheet it ended up being an entire conference of experts from all over the world. That's rarely needed at that level to respond. But I'm sure he will make a wise decision about who needs to——

Mr. BURTON. Well, the experts have been picked, have they not, to review that fact sheet?

Dr. HOOVER. I don't know.

Mr. BURTON. Well, could we make a request here today, and I'd like to put that in writing, that we have a list of the experts that are reviewing that fact sheet for accuracy and balance?

Dr. HOOVER. Sure.

Mr. BURTON. But you don't know right now?

Dr. HOOVER. I don't know.

Mr. BURTON. What are the NCI procedures for public and outside comment on the fact sheet?

Dr. HOOVER. Well, as I mentioned, people—most of the fact sheets that involve—I shouldn't say most. Many of the fact sheets, when they're developed, are also passed through our consumer panel, the cancer advocacy groups that are represented at NCI at the initial stage. Second, when someone has a concern about our fact sheet, and they e-mail us or they phone us, almost always if it's a responsible question or a responsible concern, it ends up in some sort of a review at some level.

Mr. BURTON. One of the principal studies cited by NCI refuting the contention that SV40 is in fact present in human cancer tumors was a multi-laboratory study conducted by Dr. Strickler and Dr. Shaw and published in 2001. In 2002, excerpts from a sworn deposition by Dr. Shaw were published in the journal Anti-Cancer Research. Those excerpts indicated that Dr. Shaw was under con-

tract from several pharmaceutical companies to assist them in litigation against patients with SV40 positive tumors. Dr. Strickler and Dr. Shaw published a rebuttal in the journal Anti-Cancer Research in 2003. The subcommittee understands that several NCI scientists sit on the editorial board of Anti-Cancer Research. When we asked about their apparent conflict of interest in our letter to NCI dated October 10, 2003, NCI replied via a footnote that they were unaware of Dr. Shaw's purported relationship with the pharmaceutical industry until we mentioned the issue in our letter.

When Dr. Shaw or any scientists signs a contract with NCI to conduct research either as grantee or subgrantee, are they required to disclose their conflicts of interest?

Dr. HOOVER. I think the—testifying as an expert witness, I don't believe it is asked of grantees or contractees, but I could stand to be corrected if——

Mr. BURTON. You know, that's something that needs to be corrected.

Dr. HOOVER. No, no, it's not. It is not.

Mr. BURTON. You know that needs to be changed. You know we had the advisory committees that approve or recommend to the FDA the approval of a vaccination to be put in the market. We investigated and found that there was at least one incident, I believe several, where people on those advisory committees had stock in companies that were making the very same product. And that is definitely going to, in many cases, skew somebody's judgment and is a conflict of interest.

And the thing that bothers me about—I think it was a retrovirus. What was that—RotaShield, the RotaShield vaccination. One of the people, I think it might have been even the chairman of the advisory committee, had stock in a company that was going to make that RotaShield vaccine, at least one of them, and they approved it even though a lot of the members weren't there. And the FDA went ahead with it. And the FDA always—we have found no cases where the FDA doesn't approve the recommendation of the advisory panels, and they put it in the market. At least one child died and several others were injured severely by the vaccination and it was withdrawn 11 months later. Now, that is tragic. If there's a conflict of interest in any of these areas, it must be known because if not, you're liable to put things into the marketplace and into people's bodies simply because of money, and that shouldn't happen.

Dr. HOOVER. That's not my area of expertise, but I have just two comments to make. As you know, if you work for the government, you have to fill out all those forms about what stocks you hold and those rules have never been applied to grantees. My guess is that if you suggest applying those rules to grantees that there would be a very large outcry from the academic community that this is something that they don't believe is necessary. But if that's what you want to suggest, I can——

Mr. BURTON. Well, let me interrupt you just a second, Dr. Hoover, and I apologize for this. Dr. Shaw, he gets paid to testify, and his testimony carries a lot of weight because of his expertise, and he had a conflict of interest. Don't you think that's something that could skew a report that's very, very important?

Dr. HOOVER. I personally don't. I'm sure that——

Mr. BURTON. You don't think so?

Dr. HOOVER. I'm sure that in these same cases the people who have found SV40 in tumors have also probably testified as expert witnesses because they are experts. And I actually don't believe that influences the science. One of the great things about working in the scientific field is that nothing is ever done based on one person's study or one person's research. The sine qua non in science is that it has to be replicated and it has to be replicated multiple times by different people working in different circumstances. So it is usually readily apparent if someone found something that cannot be replicated, came to a finding that can't be supported, it becomes readily apparent and it doesn't get disseminated. So I think there's actually—the way science operates, it operates in a way which irregardless of the personalities involved, guards against——

Mr. BURTON. Dr. Hoover, you're a very bright fellow. There's an old saying. Money talks and baloney walks. I'm being nice about that comment. The RotaShield virus vaccine I talked about, it was evident, and there were—the man on the advisory committee who had a conflict of interest stood to make a lot of money out of that.

Dr. HOOVER. It's possible that being on an advisory committee—and I know that FDA advisory committees require people to list conflicts of interest. I'm talking about doing research.

Mr. BURTON. OK. Well, even doing research——

Dr. HOOVER. Doing and publishing your research.

Mr. BURTON. I think it's important that there be disclosure, and I don't know that would be a discouragement. You might have to get another expert or scientist who doesn't have a conflict in that general area. But it seems to me when you're talking about something as important as SV40 and the way our scientific community and our agencies view it, that you'd want to make sure that the person doesn't have a skewed point of view because of financial interests.

How did NCI not know about this conflict until our letter dated October 10 if several NCI scientists sit on the editorial board of the Anti-Cancer Research? Because it isn't required?

Dr. HOOVER. That's correct.

Mr. BURTON. OK. So just simply because it isn't required?

Dr. HOOVER. Right.

Mr. BURTON. What is NCI planning to do to address this issue in the future, or is it NCI's position that such conflicts of interest are not serious? I think you've answered that. You don't think it's a serious problem?

Dr. HOOVER. I don't think this is a serious problem. I believe that we can have conflicts in science that are most often the results of the science and not because of incompetence or venality on the part of the investigators.

Mr. BURTON. Or money?

Dr. HOOVER. Or money, that the weight of the scientific evidence is based on multiple people finding the same thing, and the consistency of the evidence, and we have plenty of safeguards. I think there's—if we ruled out everybody who gave expert testimony in some of these tort cases, my guess is—and we ruled out giving money to them from the Cancer Institute of Research that we

would lose many of the most valuable researchers to both sides of the controversy, and I think that would be a shame.

Mr. BURTON. The Strickler-Shaw study was originally submitted to Anti-Cancer Research, one of the preeminent cancer journals, for publication but was rejected; is that correct?

Dr. HOOVER. I don't know. That's probably true. It could be true, I don't know.

Mr. BURTON. Well, it was correct. It is correct. Can you explain why a journal would reject a paper of that type?

Dr. HOOVER. A whole variety of reasons. I think I've—probably half the papers I've published have been rejected by one first. You usually shoot high to get a paper into a very high visibility journal because it's good for your career. They're the most competitive journals or the ones that can choose from many things and they may make a priority decision that this isn't of high enough interest for them to publish in their journal.

Mr. BURTON. Well, we also understand that five coauthors of the study disassociated themselves from the paper's conclusions, including Dr. Janet Butel, who actually wrote the last version of the manuscript. Is that correct?

Dr. HOOVER. Yes, it is.

Mr. BURTON. Is it common for coauthors to disassociate themselves from their own work?

Dr. HOOVER. No, it is not.

Mr. BURTON. Well, why is that? It's not common?

Dr. HOOVER. It's not common.

Mr. BURTON. Given the controversy surrounding this study, is it appropriate for the NCI to continue to use this material as the basis for the assertion that SV40 is not present in human tumors?

Dr. HOOVER. I don't think we make that assertion. We say that study is one that didn't find it; and there's, as you mention, a whole body of studies out there that don't.

Mr. BURTON. Are there other studies that say that SV40 was not found in human tumors?

Dr. HOOVER. There are maybe 10 to 13 that don't find them in some of the identified tumors. But for that particular article they submitted a letter to the editor pointing out their concerns, and Dr. Strickler responded. That is in the—published in the journal; and I believe that evidence makes it possible for people to read the article, read the concern, read the response, and come to their own conclusion of how scientists can come to their own conclusion about what it is, about whether the study would be credible and worth considering.

Mr. BURTON. The October 2002, Institute of Medicine report on SV40 contamination of the polio vaccine recommended that the Federal Government develop sensitive and specific serologic tests for SV40. Since it's now been over a year ago that the IOM issued the report, what steps has the NCI taken to implement this recommendation?

Dr. HOOVER. I do know there are people who are attempting to develop new serologic tests using viruslike particles and that Hopkins is one, and you probably know more about it than I?

Ms. WONG. Gee, Denise Galloway at Seattle and Bob Garcia, in collaboration with the city, who's with Dr. Shah's group at Hop-

kins, they are trying to develop a serological assay, but, unfortunately, I think there are problems. They could not detect anything. One possibility is that SV40 cross-reacts with these human poliomaviruses, J, C, B and K, so that might mask the detection. So I know several groups are attempting to further develop this or use other immunological assays to try to see if they can develop a more sensitive way to detect SV40.

Mr. BURTON. So the NCI is taking steps right now to implement that recommendation?

Ms. WONG. Well, unfortunately——

Mr. BURTON. No, no.

Ms. WONG. Oh, OK.

Mr. BURTON. Is the NCI taking steps to implement that recommendation?

Ms. WONG. Well, we're funding it indirectly, let's say. We're not directly funding that work.

Mr. BURTON. Why not?

Ms. WONG. Well, because—one reason is they haven't come in with a proposal to request for money. That's usually the normal route of how we fund applications, is people have this idea, they come in, it gets peer-reviewed, and if this did well and was with——

Mr. BURTON. Well, pardon me for interrupting——

Ms. WONG. Right.

Mr. BURTON [continuing]. But what we're trying to find out is what steps the NCI has taken to implement that recommendation. Have they let people know this is something that they're interested in?

Ms. WONG. Yes.

Mr. BURTON. Because the IOM in October of last year indicated, over a year ago, that those tests should be taken.

Ms. WONG. Well, at least, I know, through communications, not through any funding mechanism, we have our grantee—so-called extramural investigators are aware that this is what needs to be done in the community and this is a high priority. Unfortunately, we are not currently funding any of those studies.

Mr. BURTON. Well, it's been reported over a year ago, and it doesn't appear that there's real concern over there if over a year later they still haven't taken steps to implement the report.

Dr. HOOVER. I think what May was trying to say was that when august bodies make recommendations people that have good ideas in this area usually immediately submit grants, because they know—in fact, they reference the recommendation; and study sections who review that take that quite seriously because this is recommended in the field. And people who are out there, who are—who do this for a living—so, usually, when you don't get a sudden flood of good grant requests, it means that no one actually has a very good idea right now about how to do it better.

I suspect what's going to happen—I suspect that with all the improvement in molecular science that's going on weekly, if not daily, that somebody will come across a method that they think they can apply to this; and I would guess that the grant would come in almost immediately.

Mr. BURTON. Do you publish on the Internet or through medical journals that this is something that you want to see NCI do? I just wonder how many researchers even know that this is something——

Ms. WONG. Well, last year I had published a workshop report. In that workshop report one specific topic was on SV40, and we did recommend one for future studies in development was to develop more sensitive assays, and that could be in the workshop report. But, other than that, I don't think there's any.

Mr. BURTON. Do you think we also need an agreement on methodologies between intramural and extramural research so when examining the link between cancer and SV40 all the researchers and scientists will accept the findings once they're completed?

Dr. HOOVER. I think that the ideal would be to find methods that are robust enough that everyone can use them and everyone can get the same answer when they use them. That's been the history of when we advance.

Cervical cancer field's a good example. Back in the early 1980's, it was Dr. zur Hausen and others developed papilloma virus in the vast majority of cervical cancers, maybe 80, 90 percent. The next question was, well, how does that compare in different populations and how does it compare to people who don't have cervical cancer?

The first study that was done was to look at the—at something called block analysis, which was considered the gold standard, and looked at it in multiple labs and found there was no consistency—people couldn't replicate each other very well—and probably explained why some of the studies in humans—in human populations were giving conflicting results.

Shortly thereafter, two new assays were developed, PCR-based and a hybrid-capture-based assay, that, when used by multiple people, everybody got the same answer; and it catapulted that research forward. So now we, in fact, know that papilloma virus is the major cause of certain invasive cervical cancers. So as the field advances and as techniques get better what we try to find is a technique that everyone can use and end up getting the same answer and, hopefully, that's the right answer, that's the valid answer, as well.

Mr. BURTON. So I presume that's a yes.

OK. The October 2002, Institute of Medicine report on SV40 contamination of the polio vaccine recommended that the Federal Government develop sensitive and specific serologic tests for SV40. Since it's now been over a year ago that the IOM—oh, excuse me. I'm getting punchy here. The IOM report also recommended the development and use of sensitive and specific standardized techniques for SV40 detection. What steps has the NCI taken to implement that recommendation?

Dr. HOOVER. Once again, that would probably be done through the molecular virology community; and I'm unaware of what new efforts are going on.

Mr. BURTON. If you don't have that answer, can you submit that to me?

Ms. WONG. Yeah.

Mr. BURTON. I mean, can you find that out?

Ms. WONG. Yeah, we can get back with you later.

Mr. BURTON. We want to find out if there are sensitive and specific standardized techniques for detection, and I'd like to know if they've implemented that recommendation, and, if not, why they haven't and when they intend to do so. Can we get that information from you?

Dr. HOOVER. Sure can.

Mr. BURTON. Thank you.

[The information referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

The Honorable Dan Burton
Chairman
Subcommittee on Human Rights and Wellness
United States House of Representatives
2157 Rayburn House Office Building
Washington, DC 20515-6143

Dear Chairman Burton:

Thank you for the opportunity to respond to the Subcommittee's follow-up questions to the November 13, 2003 hearing entitled: "Preventing another SV-40 Tragedy: Are Today's Vaccine Safety Protocols Effective?" The question of whether there is a causal link between SV40 and cancer in people is very important. Working to find an answer to this question helps to drive NCI forward in our efforts to improve methods for prevention, diagnosis and treatment, and to ultimately end the suffering and death caused by cancer. The answers to your numbered questions are provided below.

1) The Institute of Medicine (IOM) report analyzed questions about whether SV40 is a transforming virus, if SV40 can cause cancer in humans under conditions of natural exposure, and whether contamination of the polio vaccine with SV40 is responsible for SV40 infection in humans. The committee report concluded that the biological evidence is strong that SV40 is a transforming virus; biological evidence is moderate that exposure could lead to cancer in humans under natural conditions; and biological evidence is moderate that SV40 exposure from the polio vaccine is related to SV40 infection in humans.

NCI did not selectively omit any of the IOM's conclusions. Rather, the fact sheet addresses the IOM's intermediate conclusions throughout the fact sheet. NCI agrees with the IOM report's conclusion that SV40 induces tumor growth in hamsters and is, therefore, a cancer-causing virus in rodents. However, this conclusion does not directly address the central question of causality. It is well established that a significant number of people received polio vaccine contaminated by SV40. Once there is a standard blood test to identify people who have been infected versus those who have not, it will be possible to do more definitive studies by comparing the cancer rates in these two groups of people. However, large epidemiologic studies (population studies) among the age groups most likely to have received the contaminated polio vaccine have shown no evidence of increased cancer risk. The IOM report's only conclusion that directly addresses the issue of whether there is a causal link between SV40 and human cancer is the conclusion that the scientific evidence is insufficient to prove or disprove the theory that exposure to poliovirus vaccine contaminated with SV40 has resulted in human cancer. Therefore, this conclusion, along with a link to the IOM report's internet address, was included in the brief section on the IOM report in the NCI fact sheet on SV40.

All NCI fact sheets go through several layers of review. The SV40 fact sheet, like other fact sheets, has gone through an initial review by cancer communications specialists in the Cancer Information Service. This is followed by a scientific review, which most recently was conducted in April 2003 by scientific staff in the Division of Cancer Epidemiology and Genetics. After the

scientific review, fact sheets are reviewed by the NCI Office of Communications and the NCI Clearance Officer. All fact sheets undergo periodic evaluation; a new review of the SV40 fact sheet will be coordinated by the NCI Office of Communications. The Office of Communications will receive input from NCI's intramural and extramural programs, including the Division of Cancer Biology, the Division of Cancer Control and Population Sciences, and the Division of Cancer Epidemiology ad Genetics, as a means of ensuring an accurate representation of what is known about SV40 and cancer.

2) NCI agrees with the IOM that "a growing body of clinical studies reports detection of SV40 DNA in several types of tumors", and that "evidence has accumulated suggesting that SV40 is likely present in some human tumors." However, NCI also agrees with the IOM that "data on the association between SV40 and human tumors are inconsistent", and that since there is currently no resolution of the question why some laboratories detect SV40 and others do not, "the presence, specificity, and strength of the association between SV40 and certain types of human tumors remain uncertain." NCI also agrees with the IOM that if SV40 is present in human tumors, the significance is currently unknown, and could range from a "causal relationship to a passenger virus, infecting cells but causing no pathology." Once better tests are developed, and more reliable data are available, we hope to be able to address why SV40 is present in human tumors and more importantly what significance, if any, the presence of SV40 in human tumors holds with regard to development of human cancer.

As previously noted, the NCI agrees with the overall conclusion of the IOM committee that "the evidence is inadequate to accept or reject a causal relationship between SV40-containing vaccines and cancer." Therefore, the issue is still a research issue and not one impacting clinical care practices. The appropriate audience for dissemination of results is the research community, particularly those involved in the study of viral carcinogenesis. This is accomplished primarily through the usual mechanisms of peer reviewed publications in the appropriate scientific journals, as well as presentations at scientific meetings. In addition, the NCI posts summaries of published research in certain areas on its web site, and provides links to other valuable summaries, including, in this instance, the IOM report. Another means of disseminating information is through NCI-sponsored workshops that focus on specific areas of research. As the committee knows, NCI has sponsored workshops in this particular subject area in 1997 and again in early 2002.

3) In each of the fiscal years 2001, 2002, and 2003, NCI has funded research to help to determine the role of SV40, if any, in the development of human tumors. NCI spent $5.469 million in FY2001, $4.891 in FY2002, and $8.398 million in FY2003 on intramural and extramural research in this area. A spreadsheet containing specific information for each award in each of the three years is attached.

The Cancer Etiology Branch in the NCI Division of Cancer Biology is responsible for administering NCI-sponsored extramural basic virology research. A Request for Applications (RFA) sets aside funds to bring attention to a narrowly defined area of research, and to stimulate

research in this area. The Cancer Etiology Branch funded 27 SV40-related grantee projects in FY2003, developed through investigator-initiated research, mediated by the standard grant application process, and funded by traditional NIH award mechanisms. This demonstrates a strong commitment to SV40 research by the extramural community without specifically setting aside funds for an RFA.

4) The IOM determined that enough descriptive epidemiologic studies, where there was opportunity for misclassification of exposure to SV40, had been done and did not recommend additional epidemiological studies in this area until "some of the technical issues are resolved." NCI has not initiated any epidemiologic studies since the IOM report. There were several studies underway when the IOM committee was deliberating, which the committee was aware of, as they were presented to the committee orally by the investigators involved. The committee was enthusiastic that new strategies be developed to "obtain a better understanding of SV40 exposure and methods of detection" so that "more meaningful case-control studies can be undertaken to help resolve the question of causality." NCI agrees and is attempting to identify and collaborate with those developing such strategies, in order to apply them to appropriate populations in furtherance of this goal.

Additionally, I am convening a meeting of the Directors of the Divisions of Cancer Biology, Cancer Control and Population Sciences, and Cancer Epidemiology and Genetics to develop procedures that will facilitate future intramural and extramural research regarding whether there is a causal link between SV40 and human tumor growth. To that end, NCI has already taken the preliminary steps of gathering program officials from these Divisions to discuss potential areas of collaboration, and opportunities for research and development that could help to drive SV40 research forward. The Institute's senior leadership will pursue an appropriate plan that will guide both our intramural and extramural research programs in this area and ensure that the effort is coordinated across the Institute.

5) NCI is currently exploring opportunities for SV40-related research through the Innovative Molecular Analysis Technologies (IMAT) Program. The IMAT Program supports research projects to develop and carry out applications of novel technologies that will enable the molecular analysis of cancers and their host environment in support of basic, clinical, and epidemiologic research. Through this program, NCI stimulates and receives applications for research that can combine epidemiology and assay development. Efforts are being made to encourage investigators to include SV40 in studies being proposed to detect tumor-causing viruses in human tissue.

The NCI Divisions involved in SV40 research are also exploring different ways for issuing a Request for Applications for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants to develop sensitive assays for the detection of SV40 infection, along with ways to validate them. SBIR and STTR grants are award mechanisms that support the research of small businesses for the development of specific products and tools. As mentioned above, one of the goals of the meeting with the Division Directors will be to

determine what tools are lacking and the techniques that would be most useful to help address unresolved issues regarding SV40 and cancer.

NCI is actively working to identify and address all causes of cancer in order to find the means for detecting, treating, and, ultimately, preventing this disease. I hope that this information is helpful to the Subcommittee. Please do not hesitate to contact me should there be any additional questions.

Sincerely,

Andrew C. von Eschenbach, M.D.
Director
National Cancer Institute

Attachments

Mr. BURTON. The IOM report further recommended that no additional epidemiological studies be performed because of the uncertainty of knowing which individuals were exposed to SV40 made interpretation of the data problematic.

The IOM report was issued in October 2002. Yet, in 2003, the NCI released a new epidemiological study based on data from Denmark. Was this study begun before or after the IOM released its recommendation, the Denmark study?

Dr. HOOVER. Yeah, that was certainly begun before; and that was actually presented to the IOM committee. They asked for people to come who had unpublished information; and we presented that plus two others, actually, another one that was published in December as well. So they had that body of knowledge in hand when they made their recommendation.

Mr. BURTON. Can you confirm that NCI has no other epidemiologic studies currently in the works?

Dr. HOOVER. We have none of the kind that the Institute of Medicine was concerned about, following populations where you can't identify who's been exposed to vaccine, who hasn't.

Mr. BURTON. Should peer review data protocols be agreed to before further studies are funded and released?

Ms. WONG. I'm sorry?

Mr. BURTON. Should peer review data protocols be agreed to before further studies are funded and released?

Ms. WONG. No, peer review should also be reviewed, and they are.

Mr. BURTON. Excuse me just 1 second.

I think you can relax for a little bit. Now I get to go to Dr. Egan.

The U.S. Food and Drug Administration first learned about SV40 problem with the polio vaccine in 1960, is that correct?

Mr. EGAN. That's correct.

Mr. BURTON. Starting in 1961, the FDA stipulated that no lots of polio myelitis vaccine would be released in the absence of negative results of a valid tissue culture for SV40; that's correct?

Mr. EGAN. That's correct, sir.

Mr. BURTON. Prior to the requirement, millions of Americans were vaccinated with SV40 contaminated polio vaccines; that's correct?

Mr. EGAN. That's correct.

Mr. BURTON. Once the FDA released there was a problem with the polio vaccine, did the agency issue any type of recall?

Mr. EGAN. No, they did not, sir.

Mr. BURTON. Why?

Mr. EGAN. OK. Well, at this time this would have been the Division of Biological Standards at the National Institutes of Health. At that time they took this question about recall or leaving material on the market to the Polio Myelitis Vaccine Committee, their advisory committee to the NIH; and the committee weighed the risks and benefits, the risks of polio, the risks of not having the polio vaccine virus out there and the potential risk that might result from SV40 and they concluded that, on balance, from the risk benefit analysis, that it was much better to leave the vaccine on the market and not to recall it.

Mr. BURTON. Once the FDA released there was a problem with the polio vaccine, did the agency ever issue a notice to health-care providers not to use contaminated vaccine, even though it wasn't recalled?

Mr. EGAN. Yeah, I do not have any knowledge of that, sir.

Mr. BURTON. Can you find out for me?

Mr. EGAN. I will try, sir.

Mr. BURTON. Because I know, since I was a child, at that time, everybody was very concerned about polio. We knew about iron lungs and all that sort of thing, and our parents wouldn't even let us get around water outside or flies or anything.

Mr. EGAN. I shared the exact same experience. I was 12 years old when the vaccine came out.

Mr. BURTON. I understand that. But when they found out the SV40 was a possible cause of cancer in the hamsters, couldn't the—I mean, there was other ways to make the vaccine other than using that contaminated SV40 vaccine; wasn't there?

Mr. EGAN. I'm not aware of another method that was known at that time. But once the issue came to the fore, the FDA—the Division of Biological Standards did require that all vaccine be free of SV40, that it be tested for SV40, each lot of vaccine be tested for SV40, be found free of SV40 prior to release to market.

Mr. BURTON. I think we know the answer to this question from Dr. Hoosier, but SV40, if it was discovered in a major vaccine today, what would the FDA's response be and how would it differ from your response in the 1960's?

Mr. EGAN. If SV40 was found in the vaccine today?

Mr. BURTON. It would not be put on the market?

Mr. EGAN. It would not be put on the market, no, sir.

Mr. BURTON. FDA testing from the 1972 to 1976 polio vaccine questions I'd like to ask you next.

In your testimony, you mentioned that the FDA has tested live supplies of polio vaccine between 1972 and 1976 and that you found them free of SV40; is that correct?

Mr. EGAN. That's correct.

Mr. BURTON. The subcommittee understands that the FDA tested no samples prior to 1972 because no pre-1972 samples of the polio vaccine still exist; is that correct?

Mr. EGAN. They were not in our possession. I don't know whether they exist or not, but the retention samples that we had went back to 1972.

Mr. BURTON. Well, would any of the laboratories that had produced the vaccine have that?

Mr. EGAN. I don't know what their retention policies are. They might.

Mr. BURTON. Could that be requested from them so that we could be testing those?

Mr. EGAN. Yes, I'll do that.

Mr. BURTON. So, since you didn't have any of that, the FDA has no way to independently test if the polio vaccine was SV40-free from 1955 to 1972; that's correct?

Mr. EGAN. Well, that's correct. Certainly the vaccine—many of the lots of vaccine from 1955 through the early 1960's was certainly contaminated. I don't think there's any question about that.

Mr. BURTON. That it was left on the market.

How about up to 1972?

Mr. EGAN. That vaccine was tested for SV40 and found to be free.

Mr. BURTON. But the vaccine that contained the SV40 was still on the market, was it not, in 1972, or was it?

Mr. EGAN. It should not have been.

Mr. BURTON. Should have been exhausted by then?

Mr. EGAN. Exhausted. I'll have to look at what the expiration dating period was, but it was probably no more than a year or 2, couple of years——

Mr. BURTON. OK.

Mr. EGAN [continuing]. And everything released after 1961 would have been SV40 free, found to be SV40 free, so——

Mr. BURTON. If after 1961 you required the vaccines to be SV40 free, why didn't they recall the vaccines that were contaminated before that?

Mr. EGAN. OK. Again, that was the—I was not there at those discussions, but my understanding is that the—they had discussions of the risks of polio versus——

Mr. BURTON. I understand, but——

Mr. EGAN. Yes.

Mr. BURTON. I'm sorry to interrupt. Go ahead.

Mr. EGAN. That in determining—in going over those risk-of-benefit determinations, they felt it was better to leave the market—leave the vaccine on the market to prevent polio, rather than withdraw it, which would have resulted in a shortage.

Mr. BURTON. I know, but I'm saying if there's a vaccine that is SV40-free coming on the market, is being produced, you still have contaminated vaccine in the marketplace. Why didn't they recall what was left at that time? Why run the risk of infecting additional people when you have an SV40-free vaccine?

Mr. EGAN. I mean, I could only, you know, speculate, not being there, but——

Mr. BURTON. Could you check?

Mr. EGAN [continuing]. I think there was an issue of supply of vaccine, how much would be available. But I mean that's speculation.

Mr. BURTON. Could you check for the record and give us an answer to that? Because it seems to me that the manufacturers would move pretty quickly to jam up supply of free SV40 vaccine as quickly as possible; and if that's the case, they would have—it seems to me our health agencies would have said, let's get this contaminated vaccine off the market.

I understand the rationale about weighing it and saying do we want to stop polio or run the risk of possible cancer down the road. I can understand that rationale if you don't have the alternatives. But once you have the alternative why would you keep that out there? That's what I would like you to answer, if you could.

Let me get back to the pre-1972. So the FDA had no way to independently test whether the polio vaccine was SV40 free from 1955 to 1957; is that correct? They had no way to test it?

Mr. EGAN. No, they were testing after 1960 or 1961. It was the period in between——

Mr. BURTON. 1955 and 1960.

Mr. EGAN. 1955 and 1961 where it was unsuspected. Because the virus didn't harm, you know, kill the cells in which it was growing.

Mr. BURTON. Excuse me, just 1 second.

My right arm here indicated that they were getting SV40 polio vaccine off—not off the market but produced after 1961, but he tells me that there was no test to test the vaccine up to 1972; is that correct?

I'm going to let you ask this question. I want to make sure I get this correct for the record.

Mr. FAULS. I think you've already answered the first question, is that you—when studies first came out that showed SV40 in cancerous tumors, FDA went back and tested all of the samples it had of polio vaccine in its possession, which only went back to 1972, to verify again those were free of SV40. That's correct?

Mr. EGAN. One minor change. We tested a sampling of the retention samples that we had. We tested 30 monopools, and we tested 30 trivalent vaccine lots. It wasn't 100 percent.

Mr. FAULS. So you didn't test 100 percent of all the lots produced from, say, 1961 to 1972 or what you had in your possession?

Mr. EGAN. No, what we had in our possession were a number of lots that were kept in as retention samples that represented lots that were manufactured between 1972 and 1996. Of them, we chose the large sampling, which was 60 samples in total; and each and every one of those was negative to a highly sensitive chain reaction, preliminary chain reaction testing methodology that we developed. We did not have any samples that predated 1972 in our possession.

Mr. FAULS. OK.

Mr. EGAN. But there was, for every lot of vaccine, lot release testing from 1961 onward; and this was the tissue-culture-based testing.

Mr. BURTON. So in the absence of this independent testing, the possibility existed that pre-1972 polio vaccine could have been contaminated with SV40; is that correct?

Mr. EGAN. I do not believe so, because each lot of vaccine was tested in the tissue culture test, which is rather rigorous, testing in sub-culturing, looking for a cytopathic effect in the African green monkey tissue, and this was done for every lot of vaccine since 1961.

Mr. BURTON. But the FDA doesn't have any samples of the vaccine that was manufactured prior to 1972; is that correct?

Mr. EGAN. No, we did not have any in our possession. If we did, we would have gone back further.

Mr. BURTON. The samples that were tested by the FDA were under—were they under the FDA's supervision since their manufacturer was supplied by individual manufacturers at the FDA's request in 1996?

Mr. EGAN. I'm sorry. I don't understand the question? Would you mind repeating it?

Mr. BURTON. I'm going to let you ask that question.

Mr. FAULS. OK, sir. Very good.

The question gets at—and I think you answered this earlier—that the samples that you tested back to 1972 were in the FDA's possession; is that correct?

Mr. EGAN. That's correct.

Mr. FAULS. OK, so you have a clear chain of custody of those samples so that you know that they were, in fact, produced in 1972 and they weren't—they weren't, say, produced in 1996 specifically because you were going to do some retesting?

Mr. EGAN. It's a different office within the—within FDA that handles these, but they come in. They're logged in and then stored in the freezer.

Mr. FAULS. OK, but since the time of the manufacturer they've been stored there?

Mr. EGAN. Yes. Whenever the samples are submitted, along with the lot release protocol, every lot of vaccine that's released to market must be released by FDA before the manufacturer can send it out. What they will send in to the FDA after they've manufactured a lot is a lot release protocol that contains all of the testing that was done so this can be reviewed by FDA scientists to see whether it's satisfactory or not. The manufacturer, at the time that they send in this protocol, will also send in physical samples in the event that FDA wishes to do any testing on that lot, so they're sent in prior to the release of the vaccine by FDA.

Mr. FAULS. And stored at FDA?

Mr. EGAN. And stored at FDA.

Mr. BURTON. And they're still there in frozen status?

Mr. EGAN. Yes.

Mr. BURTON. And you have documentation to verify that the vaccine was actually produced when the manufacturer said it was produced?

Mr. EGAN. Well, it would come in——

Mr. BURTON. Come in with it?

Mr. EGAN [continuing]. With the lot release protocol at that time. So the vaccine that was manufactured, for example, in 1982 would—that vaccine would come in with the lot release program.

Mr. BURTON. What we're trying to get at is something that was produced in 1972 is there as a 1972 product and not something that was manufactured later in 1994?

Mr. EGAN. No.

Mr. BURTON. OK. Thank you.

Mr. EGAN. No, that would not be an issue.

Mr. BURTON. Has the FDA required the polio vaccine manufacturers to produce results showing that their seed stocks are SV40 free?

Mr. EGAN. The two vaccines that are currently in use—you know, we've switched, a number of years back, to IPV—and the two major IPV's that are in use at the moment——

Mr. BURTON. Are SV40 free.

Mr. EGAN. They're SV40 free, but the manufacturers also demonstrated that the seeds that are used to produce the vaccine are SV40 free by PCR technology, and I'm referring to the recently licensed Pediarix and the Ipol.

Mr. BURTON. So the manufacturers are required to submit their polio vaccine lots to a 14-day tissue culture procedure to test for the presence of SV40?

Mr. EGAN. OK, the procedure that I think—I think the procedure that you're referring to is, for example, the one that was in the Code of Federal Regulations. If I look at the one, for example, for OPV, they hold the seed—they hold the part of the production for a number of days—I forget how many it is, exactly—and then there are two subcultures of 14 days and 14 days. So from the beginning to the end of that entire process with the control production cells is about 50 days.

For the part of the harvest with the monkeys just prior to the inoculation with polio virus, they also hold those cells and then subculture them for one or two periods of—I think it's one period of 14 days. They observe the cultures in 14 days. Then there's a third one with the actual harvest itself where they neutralize the polio virus with specific anti-sera and then culture and subculture again. So they are actually three very—three independent sets of cultures and subcultures that go out for, you know, 28 plus days.

Mr. BURTON. So that would be considered three independent tests?

Mr. EGAN. They're independent tests in the sense that they're done on different parts of the process, yes. They are not independent in the sense—they're independent tests, yes. They are coming from the same tissues, though. I would be happy to outline that for you.

Mr. BURTON. My counsel says that your original answer was they are not part of the same test.

Mr. EGAN. They are three independent tests on the same monkey kidney cells. Yes, they are three independent—they are independent tests. For clarity, I would be happy to submit to you what is done.

Mr. BURTON. I wish you would do that.

Mr. EGAN. Sure.

Mr. BURTON. I think that might help.

Mr. EGAN. I think we can diagram that.

Mr. BURTON. Like I said, we have somebody who used to be—work on this in the health department of the government, and we want to, you know, discuss this with them in some detail.

Mr. EGAN. It's very, very complicated and hard to understand.

Mr. BURTON. That's why we go to an expert. You folks tell us, and then we talk to them to find out if there is additional information we need.

Mr. EGAN. Sure.

Mr. BURTON. So we appreciate that.

Well, I think this is important. There's evidently one scientist who claims to have discovered a second strain of SV40 that takes longer than the 14 days to develop in the culture testing. You said that you actually go beyond the 14 days?

Mr. EGAN. That's correct.

Mr. BURTON. If a polio vaccine lot fails that 14-day test and the subsequent tests that are part of the testing process, does the manufacturer automatically destroy it or can they attempt to clean the vaccine and retest it for SV40?

Mr. EGAN. I will double-check this, but my understanding is that if SV40 is in the vaccine they are not permitted to clean it up.

Mr. BURTON. If they want to get rid of it, they destroy it.

Mr. EGAN. Yes, if SV40's in the vaccine, yes.

Mr. BURTON. Can you double-check that for us?

Mr. EGAN. Yeah, but that's my interpretation, my understanding.

Mr. BURTON. Well, one of the accusations against one of the major drug manufacturers of the product is that they went back and scrubbed it and used the same vaccine, so we'd like to check that if you could for us.

Mr. EGAN. Yeah, I'd be very happy to. I do not believe that's allowed.

Mr. BURTON. Would you know if they did that?

Mr. EGAN. It would have to be part of the manufacturing record, yes. Any reprocessing——

Mr. BURTON. One of the accusations we have been told is that they—that this rescrubbing process did take place. Could that have been done without the FDA's knowledge?

Mr. EGAN. Anything is possible. The only reprocessing that I'm aware of is related to the viral inactivation, and that's described in the CFR.

Mr. BURTON. OK.

Mr. EGAN. That's the polio virus inactivation.

Mr. BURTON. I guess if we were to find out that a manufacturer did clean and retest they'd be subject to penalties by the FDA, severe penalties; wouldn't they?

Mr. EGAN. I cannot really respond to the compliance side of that, what those penalties would be.

Mr. BURTON. Is there any way we can find out what those penalties would be if that was the case?

Mr. EGAN. Yes.

Mr. BURTON. So you will let us know the maximum penalty for violating those regulations. And the manufacturers are required to, by the FDA, to keep records on all testing of vaccine prior to releasing it to the public; that's correct?

Mr. EGAN. Yes. I believe that they are required to keep those records for—it's either 5 years or 10 years after the date of manufacture. I don't know—I think it is one of those. They are required to keep them for either 5 or 10 years after the date of manufacture. We're going to have to look it up and get back to you on the exact length of time they're required to keep them.

Mr. BURTON. I appreciate that.

Are experimental monkeys ever allowed to be used as donor tissue for vaccine growth cultures?

Mr. EGAN. Monkeys that had been used in experiments?

Mr. BURTON. Mm-hmm.

Mr. EGAN. No.

Mr. BURTON. I guess that's another accusation that's been made, and we'd like to verify that, and we would probably—you would have to go to the manufacturer to get that information; would you not? How would the FDA know about that?

In 1986, I think it was Wyeth-Lederle wrote to the FDA, talking about a herd of monkeys that they had, that they wanted to, I

guess, reuse. Can you see if there's any correspondence or any information on that we can get about that?

Mr. EGAN. 1986 was reuse of monkeys from Wyeth?

Mr. BURTON. Wyeth Lederle material, yeah. I presume that if that was done that also would be subject to review and penalty by the FDA, if they were doing that?

Mr. EGAN. Again, I'll have to check this, but I think that the Code of Federal Regulations states that monkeys that had previously been used in some fashion——

Mr. BURTON. Can't be.

Mr. EGAN [continuing]. Cannot be used.

Mr. BURTON. Well, you will let us know the maximum penalty of what it would be if it did occur?

Mr. EGAN. Well, yeah. I won't personally, but I'll ask the compliance, yes.

Mr. BURTON. Thank you.

Mr. EGAN. Because I don't know that part of this.

Mr. BURTON. How often does the FDA conduct site visits to inspect vaccine manufacturing facilities?

Mr. EGAN. Those are generally biennial.

Mr. BURTON. Biennial?

Mr. EGAN. Yes, sir.

Mr. BURTON. Every 2 years?

Mr. EGAN. Yes, sir.

Mr. BURTON. Are they usually announced or not announced?

Mr. EGAN. They are at least now unannounced. I don't know if in the past what the policy was, but they're unannounced.

Mr. BURTON. Is there any way we can find out what the policy has been and what it is now?

Mr. EGAN. Yes.

Mr. BURTON. And when it was changed?

Mr. EGAN. Yes.

Mr. BURTON. Thank you.

How often does the FDA review their regulations to be sure they conform to the most current good manufacturing processes? I presume you do that periodically; don't you? Review your regulations to make sure that——

Mr. EGAN. Well, the current good manufacturing practices regulations that exist are, let me say, more philosophical. They state how things should work as opposed to what exactly everything is. For example, like a housing code may say you have to use exactly this kind of wire, you know, in a co-axial cable. It doesn't say that. It says that, you know, records must be maintained, personnel must be trained, etc., and that this is constantly evolving.

Mr. BURTON. So it's a flexible approach?

Mr. EGAN. It's a flexible system.

Mr. BURTON. But records are kept?

Mr. EGAN. Oh, yes.

Mr. BURTON. OK.

How often are the FDA inspectors retrained in inspecting for good manufacturing practices or are they retrained? I mean, you know, if you're an insurance man or a lawyer or real estate guy, a lot of the professions, they have an educational process, because they have that for the inspectors.

Mr. EGAN. Yeah. The inspectors for good manufacturing practices facilities and inspections, these are actually done by a different part of the agency than the Office of Vaccines, so I'll have to get back to you on that answer, but I believe that they are given training in the beginning and that there's continual updating.

Mr. BURTON. Continuing education?

Mr. EGAN. Continuing education.

Mr. BURTON. Well, if we could get that, that would be helpful.

If a manufacturer is found to be in violation of FDA regulations, what can the agency do to the manufacturer? Can they close them down or penalize them? What do they do?

Mr. EGAN. I'll have to get the lawyers to——

Mr. BURTON. OK.

Mr. EGAN [continuing]. To give you exactly what those are, but we can certainly suspend or revoke the license.

Mr. BURTON. I did know we were talking about the vaccination for anthrax, and the major manufacturer was shut down for a while because of some problems like that. We'd just like to know what the rule of—that you follow to deal with that.

Has the FDA ever taken any action against any of the FDA's licensed polio vaccine manufacturers? If you don't know——

Mr. EGAN. I don't know.

Mr. BURTON. OK.

In May 2000, the FDA's Public Health Service and the Center for Biological Study and Evaluation held an advisory board meeting to review vaccines and other biologically related agents. At the board meeting, advisory board Chairman Harry Greenberg admitted that there's no way to ensure absolute purity in the vaccine manufacturing process. Is that a pretty accurate statement?

Mr. EGAN. Yes.

Mr. BURTON. Chairman Greenberg also stated there was no way possible to eliminate all infectious adventitious agents, which SV40 would be one example of. Is that a correct statement as well?

Mr. EGAN. Well, you know, if we want to talk about, you know, adventitious agents' molecules, ensuring that something is out to the last possible molecule or the last, you know, virion is essentially impossible.

What one does is, you know, as the case with SV40 for the best available technology, that the materials are negative to that testing. It's impossible to go beyond the limits of scientific testing.

Mr. BURTON. I will guess this is a tough question——

Mr. EGAN. And the same, for example, if you had, you know, water and you wanted to say that the lead content of water must be, you know, approved, that there isn't one single lead molecule in the entire reservoir. It's impossible.

Mr. BURTON. Well, has the FDA ever established a threshold level for contamination for vaccines? I mean, is there a maximum level of contamination that you would accept or is that a flexible thing? Is that a judgment call?

Mr. EGAN. Right. It would be flexible, depending on the situation, vaccine materials.

Mr. BURTON. That's the way it sounds when SV40 was first found.

Mr. EGAN. With SV40, when it was first found they developed very sensitive tissue culture tests that were developed, and the answer was that there could be no SV40 demonstrated by that testing.

Mr. BURTON. So they were almost 100 percent sure there was no SV40 in those?

Mr. EGAN. We can make estimates of what the most could have been, there would have been, and it's very small.

Mr. BURTON. Is there some kind of standard that you're considering developing that would set a minimum level acceptable for these contaminants or can you do that?

Mr. EGAN. For SV40?

Mr. BURTON. No, for any kind of a contaminant.

Mr. EGAN. Well, I mean, we certainly have, you know, standards for a lot of things. For example, the amount of residual DNA in vaccines or in biological products, you know, cannot be above a certain number of picograms. So these standards are developed and used all the time.

Mr. BURTON. The bottom line is you can't be 100 percent free of contamination, you can't guarantee that, just do the best you can?

Mr. EGAN. Yes, sir.

Mr. BURTON. OK. Thank you.

What else do we have? Anything else?

We're almost finished here, and I appreciate your patience.

Mr. EGAN. You're very welcome, sir. This is a very important issue.

Mr. BURTON. It is, it is, and you know there's lawsuits pending on some of these issues.

Mr. EGAN. Yes, I'm aware of that.

Mr. BURTON. There are people who worked at the health agencies who take issue with some of the statements I've admitted, and we just wanted to make sure we clear it up.

Mr. EGAN. We have disagreements all the time.

Mr. BURTON. The IOM's SV40 report issued in October 2002—and this is a question for any of you—recommended that the appropriate Federal agencies develop a vaccine contamination, prevention, and response plan. The plan should identify the steps already in place of those that need to be developed to prevent contamination of vaccines and to respond to concerns about possible contamination. The plan should include strategies for routine assessment of vaccine for possible contamination, notification of public health officials, health care providers and the public if contamination occurs, identification of recipients of contaminated vaccine and surveillance and research to assess health outcomes associated with contamination. What have either of you or your two agencies done to implement that recommendation?

Mr. EGAN. That's being handled by the National Vaccine Program Office and specifically something known as the Interagency Group within that office, which has representatives from each of the Federal agencies that's involved with vaccines. So that plan is—that part of the recommendation of the IOM is handled by the National Vaccine Program Office.

Mr. BURTON. How far advanced is that plan; do you know?

Mr. EGAN. I'm not the representative to it, so I don't know.

Mr. BURTON. Do we need to request that information from them or could you request it for us?

Mr. EGAN. I can ask the initial vaccine program where they stand on that program.

Mr. BURTON. The last thing is, also, it's important—if a plan is developed, is there a communication program that's being formulated to inform the public and medical practitioners about it?

Mr. EGAN. That should be part of the plan. I think that is part of the recommendation of the IOM.

Mr. BURTON. OK.

Mr. EGAN. And I certainly concur with that.

Mr. BURTON. We'd like to know about that, as well.

Is there anything else we need, right now?

I want to thank you very, very much for your patience. I'm sure we'll be talking in the future, but you're very helpful, and we appreciate it.

I would really like to get from the two of you, you know, a proposal or whatever you want to call it that would help in getting additional funding and the cross-pollination of the agency so that we could maybe get to the conclusion a little bit quicker on cancer.

OK, hey, thanks a lot. We appreciate it.

Mr. EGAN. You're very welcome, Mr. Chairman.

Mr. BURTON. We stand adjourned.

[Whereupon, at 4:45 p.m., the subcommittee was adjourned.]

[The prepared statement of Hon. Elijah E. Cummings follows:]

Statement of Congressman Elijah E. Cummings
Government Reform Hearing
On
"Preventing Another SV40 Tragedy: Are Today's Vaccine Safety Protocols Effective?"
November 13, 2003 at 2:00 p.m.

Thank you, Mr. Chairman.

I want to thank you for holding this hearing as a follow-up to the Subcommittee's hearing on September 10, 2003, entitled "The SV-40 Virus: Has Tainted Polio Vaccine Caused an Increase in Cancer?" During that hearing, many discomforting issues surrounding the Simian Virus 40 (SV-40) and its possible presence in U. S. polio vaccines that were distributed through the year 1962 were discussed. I hope this hearing sheds more light on and offers solutions to the problem of the tainted polio vaccine.

Over the years, and since I have been a member of this committee, we have held several hearings on the issue of vaccinations, ranging in topic from the adverse reactions to vaccinations, the Vaccine Injury Compensation Program (VICP), vaccinations for our military personnel, to the Federal Drug Administration's (FDA) regulations of vaccines. I think most of us would agree that vaccinating against infectious diseases has been one of the most

effective public health initiatives ever undertaken in the United States. Vaccines have reduced vaccine-preventable diseases including measles, mumps, and polio by more than 95%. I support vaccinations, as they are responsible for the eradication of many common deadly diseases in this country.

Unfortunately, despite the benefits, vaccination programs can carry a human cost. The U.S. Government acknowledges that vaccines can have side effects, including death or disabling conditions requiring lifetime medical care. These reactions can be devastating to affected families.

In response to the growing concerns surrounding vaccinations, especially childhood vaccinations, in 1986, the National Childhood Vaccine Injury Act established the Vaccine Injury Compensation Program (VICP) – to compensate individuals, or families of individuals, who have been injured by childhood vaccines, whether administered in the private or public sector. The program has been successful in its policy goals of ensuring vaccine supply and establishing a program for individuals and families injured by childhood vaccines. The establishment of programs such as the Vaccine

Injury Compensation Program, prove Congress' commitment to addressing concerns about the potentially damaging side affects of vaccines.

With the continued widespread use of vaccines, along with state mandates requiring vaccination of children for entry into school, college or day care it is important that the federal government continue not only vaccine production, but also vaccine research, in order to improve existing vaccines and develop new ones. Vaccine safety research must continue to be a top priority, including working to eliminate adverse reactions.

Congress cannot guarantee the 100% safety of vaccines, but by holding hearings such as this one, we can hopefully address past and present issues related to the distribution of contaminated vaccines, such as the polio vaccine distributed prior to 1963 with SV-40. By looking at the government's past experience with a contaminated vaccine, we can hopefully address some key concerns and make sure that history does not repeat itself. Congress must make sure that innocent citizens are protected from another SV-40 tragedy. The repercussions of such an occurrence are much too damaging to our citizens, so we must discuss our current safety

protocols in an effort to measure their ability to both effectively prevent and deal with future instances of tainted vaccines.

Once again, thank you, Mr. Chairman, for holding this important hearing. I look forward to hearing from all of our witnesses today as we discuss ways in which we can prevent another SV-40 tragedy, as well as, enhance and implement current vaccine safety protocols.

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